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Is Baseline Health-Related Quality of Life Predictive of Survival Time for Patients with Advanced Primary Lung Carcinoma?

by

Melina W. Dharma-Wardene

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Public Health

Department of Public Health Sciences

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled *Is Baseline Health-Related Quality of Life Predictive of Survival for Patients with Advanced Primary Lung Cancer?* submitted by Melina W. Dharma-Wardene in partial fulfillment of the requirements for the degree of Master of Public Health.

To My Parents,

"Where there is love and inspiration,

You can't go wrong"

-Ella Fitzgerald

ABSTRACT

OBJECTIVE: Retrospective evaluation of the association between baseline patient-reported heath-related quality of life (HRQL) and survival of patients with advanced primary lung carcinoma. **PATIENTS & METHODS:** Patients (n=42) were accrued (1997-1999) prior to undergoing chemotherapy at the regional cancer center. Demographic, clinical data were obtained; HRQL was measured using *FACT-G* scores. Descriptive statistics, Cox and Kaplan-Meier procedures were used in analysis. **RESULTS:** Baseline *FACT-G* scores predicted survival (p=0.004), when controlling for standard clinical factors. In addition, covariates histology (p=0.006), stage (p=0.0006), sex (p=0.04) and previous weight loss (p=0.03) were confirmed as independent predictors. Median survival was 9.87 months; four patients were alive at last assessment (March 31, 2001). **CONCLUSIONS:** Baseline *FACT-G* and survival were associated with statistical significance, controlling for previous weight loss, sex, histology and stage. HRQL may have merit as a stratification criterion in clinical trials, further informing treatment decisions. Patients who have low baseline HRQL may be spared the toxicity of aggressive therapy. Further investigation appears to be warranted.

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I. INTRODUCTION

There has been increasing interest in the concept of health-related quality of life (HRQL) of cancer patients. HRQL measures have predicted patient survival for multiple pathologies including malignant melanoma(1), ovarian (2), breast (3), and lung (4) carcinoma. It has been suggested HRQL may be preferable to the traditional predictors of survival time- tumour size and response to treatment (5). Although studies have been conducted previously, this relationship warrants further investigation, specifically in the context of lung cancer.

In Canada, lung cancer is the leading cause of cancer mortality. It accounts for almost 30.8% of all cancer-related deaths in males and 24% of cancer deaths in females (6). The prognosis for advanced lung cancer is poor with an approximate 13% overall 5-year survival rate (6). Most epidemiological research has focused on identifying modifiable risk factors to prevent cancer development. For diagnosed patients there have been only modest advancements in treatment and HRQL is a concern. By definition, HRQL is the extent to which a "patient's usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment"(7). Measuring HRQL can be seen as assessing more than biological factors, including the patient's perspective as well as physical, mental, and social domains.

Multiple studies have investigated the relationship between HRQL and survival. To date, most have focused on HRQL as a measure of process and outcome in longitudinal studies. Less work has been done on its role as a predictor of survival. The proposed research further investigates the question "is baseline HRQL predictive of survival for patients with primary advanced lung carcinoma?"

The specific objectives of the study were:

1. To examine baseline HRQL as a predictor of survival time for patients with advanced primary lung cancer. Specifically, while controlling for known clinical and demographic covariates, this association will be examined using scores from the *Functional Assessment of Cancer Therapy- General (FACT-G)* version 3, a core instrument from the *FACT-Anaemia (FACT-An)* questionnaire.
2. To determine whether baseline HRQL is an important predictor of patient's response to treatment. Baseline scores of the *FACT-G* questionnaire and standard definitions of response to treatment will be used to investigate this association, controlling for standard clinical factors.
3. To determine whether change in a patient's well being (measured as a change in *FACT-G* scores from baseline to terminal point of measurement), is associated with baseline *FACT-G* score. True association between baseline FACT-G scores and change in FACT-G scores will be investigated, controlling for standard clinical factors.

A retrospective cohort design was used in the examination of the hypothesised associations. A cohort of 42 patients seen in outpatient clinics at the Cross Cancer Institute (CCI), Edmonton from October 1997 to February 1999 was followed. Originally, these patients were accrued for the exploratory, descriptive study *Fatigue in Patients Undergoing Chemotherapy* (8). Using the *FACT-An* questionnaire, patient HRQL was assessed prospectively at baseline and over the course of chemotherapy. In the HRQL study, *FACT-G* scores will be used to measure HRQL. In addition, data on standard clinical variables that are recognised as important predictors of survival will be

used in the analyses. These variables include *Eastern Co-operative Oncology Group (ECOG) Performance Status Rating*, histology, clinical stage, age, sex, hepatic metastases, and previous weight loss.

In summary, this study was designed to evaluate the effectiveness of patient-reported baseline HRQL as a prognostic indicator. If baseline HRQL predicts survival, it may assist in clinical management and may have merit as a stratification criterion in future clinical trials.

II. LITERATURE REVIEW

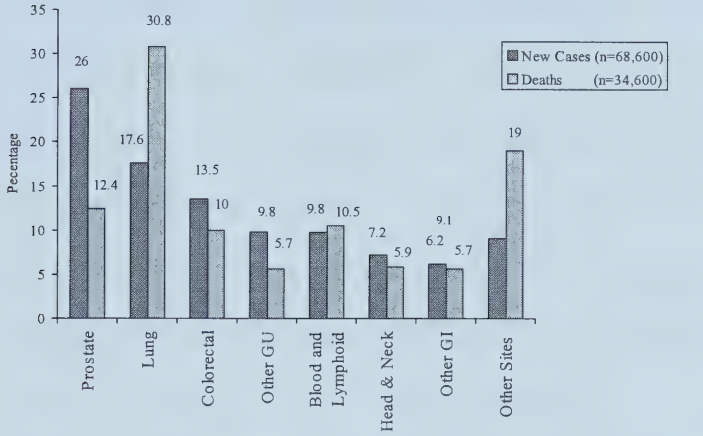
A. Lung Cancer: The Burden of Illness

In the Western world, lung cancer is a major public health concern. In 2001, 15.6% of all new Canadian cancer cases (excluding non-melanoma skin cancer) were diagnoses of primary tumours in the lung. This is an incidence rate of 127 per 100,000 (rates are age-standardised to the 1991 population), the highest for any cancer site (6). When dichotomised by gender, lung cancer is second in incidence to carcinoma of the breast in females (29.8%) and to prostate cancer in males (26.0%)(6) (Figure 1 and 2).

Furthermore, lung cancer is the leading cause of overall cancer mortality, comprising almost 32% of all disease specific deaths in males and 25% in females. In 2001, an estimated 20,400 incident cases were diagnosed of which 82% or 17,500 will be fatal (6). In patients with localised disease, the overall 5-year survival is only 30% for males and 50% for females (9). For advanced cases there is a 13% overall 5-year survival rate (10).

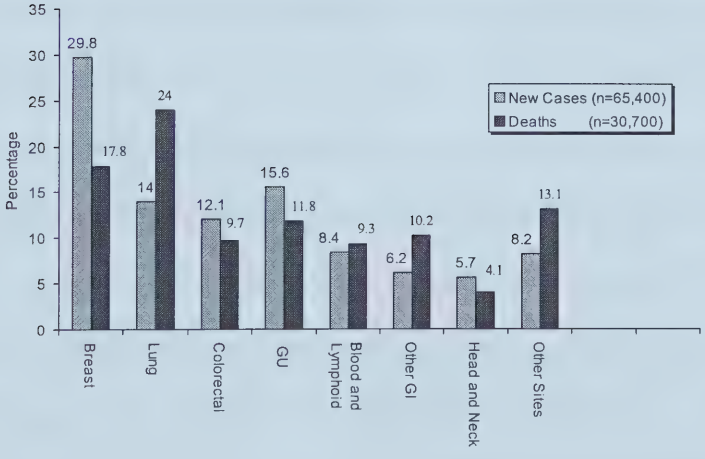
Epidemiologic research on lung cancer has focused on identifying modifiable risk factors to prevent cancer development. However, for patients already diagnosed or having progressive disease, treatment advancements and benefits have been modest. These individuals commonly experience not only symptom distress and decline in physical functional status but diagnosis and treatment also engender multiple complex psychosocial phenomena. While symptom palliation maybe a key component to any intervention, the psychotherapeutic impact of these phenomena may be reflected in assessments of emotional well-being and overall HRQL.

Figure 1: Percentage Distribution of Estimated New Cancer Cases and Deaths for Selected Cancer Sites in Males, Canada 2001



Source: National Cancer Institute of Canada 2001

Figure 2: Percentage Distribution of Estimated New Cases and Deaths for Selected Cancer Sites in Females, Canada 2001



Source: National Cancer Institute of Canada 2001

B. Health-Related Quality of Life (HRQL)

Over the last decade, the role of patient-reported HRQL assessment has gained importance. This is reflected in a voluminous and growing body of scientific literature on HRQL in medicine, in general, and specifically, in cancer.

HRQL is defined multiple ways: as "patients' appraisal of and satisfaction with their current level of functioning compared to [what is perceived to be] the possible ideal" (11), as "an individual's overall satisfaction with life and their general sense of personal well-being" (12) or as "a composite of physical, emotional, and social functioning as well as negative aspects of somatic discomfort and other symptoms produced by a disease or its treatment" (13). Regardless of specificities, there is wide consensus that HRQL includes both objective and subjective components (11, 13-15) and is a multi-dimensional construct, aggregating "those parts of general quality of life that relate directly to an individual's health, [including] domains of physical, psychological, social, spiritual, role functioning, as well as general well-being"(16). This definition encompasses the minimum requirements for HRQL measurement: the patient's perspective and capturing physical, emotional and social well-being.

In this study, recent publications (1990-2001) examining HRQL and survival by lung cancer patients were identified through Medline, CancerLit, and PubMed literature searches using the keywords quality of life, health-related quality of life, survival, prognostic factors, and lung neoplasms. The key words 'quality of life' and 'lung neoplasms' were used create an initial database of articles for review. These articles were then categorized and sorted by combining the initial search strategy with more

specific descriptors ('prognostic factors' and 'survival.') The initial literature search was carried out in 2000 and updated twice in 2001 and once at the end of July 2002.

After review, articles relating to cancer genetics, the pharmacology of therapeutic regimens and psychosocial causes of lung cancer (including psychosocial risks for smoking) were eliminated. Additional studies known to the author through prior searches were added; these results were most useful when including comparable studies with more than one tumour type or those studying carcinomas other than lung.

Baseline HRQL scores predicted survival in patients with neoplasms of various sites including prostate (17), colon (18, 19), brain (20) and breast (3, 21). Specific symptoms were often associated with shortened survival time across multiple pathologies. Poor scores for physical well-being, mood, appetite, nausea and vomiting (but not pain) scales as well as low overall HRQL were significant predictors in patients receiving treatment for metastatic malignant melanoma (22) and metastatic breast cancer(1, 21). In patients with ovarian cancer, Kornblith et al.(2)noted that pain, impaired physical function, and heightened psychological distress was an important symptom constellation predictive of overall HRQL and subsequent survival (23).

In patients with metastatic lung cancer, baseline HRQL scores are also predictive of survival. Statistical significance remained after controlling for initial performance status, weight loss, stage of disease, number of metastatic sites and type of treatment(4, 24). Some studies (25) have reported that severe pain was a predictor of shortened survival, while others have shown that increases in pain precedes the development of more burdensome physical symptoms (26, 27).

HRQL prognostic indicators for survival in lung carcinoma have included specific focus on psychosocial domains. Unlike many other cancers, patients with lung carcinoma may have an increased occurrence of psychiatric disorder or personality change due to the presentation of brain metastases as a first indication of disease onset (28). In addition, elevated anxiety and depression can present upon learning of the diagnosis and seriousness of the disease, even though clinical levels are rarely approached (29-31). Disease and treatment-related symptoms of lung cancer like fatigue, anorexia, and sleep disturbances may mask symptoms of deeper depression (32, 33).

A handful of studies have found that specific social domains are associated with differences in patient survival time. Ganz et al.(4) found married lung cancer patients had a higher baseline HRQL and reduced mortality compared to unmarried patients. Other literature report symptom distress is exacerbated for women, the poor, and those with lower socioeconomic status (34, 35) leading to poorer HRQL and, in some cases, shortened survival.

However, HRQL measurement can be prone to limitation when findings are limited by small sample sizes and missing data (4, 24). Longitudinal data after the cessation of treatment are rare. In addition, results indicate a lack of consistency in the association between HRQL and survival. Ringdal et al.(36) found psychosocial variables were predictive of survival when examined individually, but when included in a statistical model, psychological variables did not add prognostic value. Herndon et al.(25) found that after adjustments for significant clinical factors, (*ECOG*, histology, dyspnea, weight loss, albumin level and adrenal metastases), the global measure of HRQL was not a statistically significant prognostic indicator in multivariate analyses.

III. PROPOSED ASSOCIATION AND HYPOTHESES

The primary hypothesis for this study is:

P_1: Individuals who have lower baseline HRQL scores have survival that is shorter by both quantitative importance and statistical significance than those who have higher baseline HRQL scores.

The secondary hypotheses are:

S_1: There is a positive association between baseline HRQL and patients' response to treatment.

S_2: There is a positive association between baseline HRQL and subsequent change in HRQL scores (reflecting a change in patient well-being) over the course of treatment.

To investigate these hypotheses the specific objectives of the study are:

1. To examine baseline HRQL as a predictor of survival in patients with advanced primary lung cancer. Specifically, while controlling for known clinical and socio-demographic covariates the nature of this association will be examined using scores from the *FACT-G* (version 3) questionnaire.

2. To determine whether baseline HRQL is an important predictor of patient's response to treatment, while controlling for known clinical factors. Baseline scores of the *FACT-G* questionnaire and standard definitions of response to treatment will be used to determine the nature of this association.

3. To determine whether change in a patient's well being, reflected in change in *FACT-G* scores from baseline to terminal point of measurement, is associated with baseline *FACT-G* score, while controlling for standard clinical factors.

Change in *FACT-G* scores is regressed on baseline *FACT-G* scores and as well on standard clinical prognostic indictors.

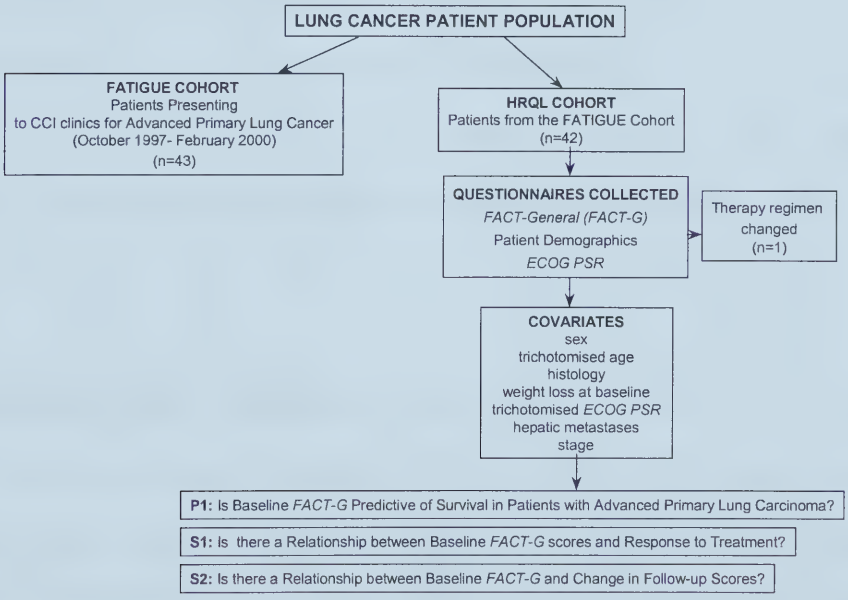
IV. METHODS

A. Study Design

1. Fatigue Study

The study *Fatigue in Patients Undergoing Chemotherapy* (8) was an exploratory descriptive pilot project (Figure 3).

Figure 3: Study Design



The Fatigue Study had 4 specific aims:

1. To determine the proportion of advanced staged lung cancer patients on platinum-based chemotherapy who have fatigue progression over the course of their treatment. The study also assessed the timing of fatigue progression in these patients.

2. Exploration of what constitutes a clinically important change in a patient's score on the HRQL instrument, *FACT-An*.

3. To determine whether fatigue correlates with the worsening of a patient's HRQL while on chemotherapy.

4. To evaluate the study design and provide information for the design of subsequent therapeutic trials (8).

Published literature suggests patients receiving cisplatinum or carboplatin-based chemotherapy for the treatment of lung cancer experience increased levels of fatigue(37-39). The independent variable was the progressive course of chemotherapy and the dependent variable was the resulting degree of patient fatigue. Fatigue scores were hypothesised to also depend on age, histology, stage of disease, hemoglobin levels, prior history of depressive mood disorder, psychosocial variables and other factors. These covariates as well as the patient's course of chemotherapy may influence fatigue progression.

2. Health-Related Quality of Life (HRQL) Study

Using a non-interventional retrospective cohort design, HRQL and survival is assessed in patients with advanced primary lung carcinoma (Figure 3). Data collected for the pilot project, *Fatigue in Patients Undergoing Chemotherapy* (8) patients undergoing treatment at the Cross Cancer Institute(CCI), Edmonton, Alberta, Canada is used to investigate the prognostic value of baseline HRQL. The CCI is a tertiary care center responsible for individuals residing in central and northern Alberta. It draws from a

population base of approximately 1.8 million, including residents of northern British Columbia, the Yukon, northwest Saskatchewan and the Northwest Territories.

The study cohort consisted of a consecutive series of 43 patients undergoing treatment from January 1997 to February 1999. The same inclusion and exclusion criteria were used for subjects in the *HRQL* and the *Fatigue Studies*. Of 43 cases accrued in the original pilot project, 42 had evaluable baseline HRQL measurements. These 42 cases are the subjects of this research.

B. Patients

1. Fatigue Study

Upon approval from the Alberta Cancer Board Research Ethics Committee, patients were accrued consecutively as they presented at the CCI. Subjects for the Fatigue Study met the following inclusion criteria 1) a diagnosis of locally advanced or metastatic non-small cell (NSCLC) or small cell(SCLC) lung cancer; American Joint Committee on Cancer/ Union International Contre le Cancer (AJCC/UICC) Stages IIIa, IIIb or IV 2) enrollment was prior to commencing a course of outpatient cisplatinum or carboplatinum-based chemotherapy 3) no radiotherapy was planned during the course of chemotherapy, although neoadjuvant radiotherapy was permitted 4) outpatient status at the CCI 5) able to read, write and speak English 6) receipt of informed consent and 7) no other major disabling medical or psychiatric conditions that substantially impaired the activities of daily living(40).

When a suitable candidate was identified, the attending physician or research nurse explained the nature of the study. Patients were given the questionnaires after

providing informed consent. The patient was then considered accrued to the study. A cohort of 43 subjects was enrolled in the *Fatigue Study.*

Baseline data collection began prior to the first cycle of chemotherapy. Patients underwent differing platinum-based chemotherapeutic regimens and number of cycles (from 1 to 8 cycles) depending on their histology, response to therapy, and tolerance of treatment toxicity.

2. HRQL Study

Forty-three patients were accrued as a single independent cohort for the original pilot project, the *Fatigue Study.* Of these patients, 42 had evaluable baseline questionnaires. One individual did not complete the package of questionnaires. These same 42 cases are the subjects of the *HRQL Study.*

C. Instruments: What are the Questionnaires?

C1. Fatigue Study

Patients were administered a multi-questionnaire package that comprehensively evaluated HRQL prior to the first cycle of chemotherapy (baseline) and prior to each subsequent cycle of chemotherapy (follow-up)(Appendix A). The final HRQL assessment was administered two to four weeks after completion of treatment.

If a patient did not present to follow up clinics and questionnaires were due to be completed, the individual or family was contacted to ascertain the next date of appointment. If the time delay was less than or equal to one week, then the questionnaires were completed upon the patient's return to clinic. If the delay was

greater than one week, questionnaires were mailed to the patient for completion with a self-addressed stamped envelope for return (40). It was noted whenever this occurred.

In the *Fatigue Study*, demographics, blood chemistries and general history were recorded by the attending physician or research nurse, while the *General Health Questionnaire (GHQ)* questionnaire was patient self-administered. Collection of this data occurred only at baseline. The *ECOG Performance Status Rating,* administered by the health professionals, and the *FACT-An,* patient self-administered, were both collected at baseline and follow up. The instruments *Physician Assessment of Patient Fatigue Level* and the *Patient Self-Assessment of Fatigue* were completed at follow up only (8).

2. HRQL Study

Two questionnaires- *FACT-An* and *ECOG* - were chosen for analysis from the instrument battery of the original study (Appendix B). These tools were selected because they were the most suitable for examining the primary and secondary hypotheses.

The *FACT-An* consists of the *FACT-General (FACT-G)* core questionnaire and an anaemia (*An*) supplement. The *FACT-G* consists of 34 Likert-type questions covering five domains- physical well- being (PWB), social/family well- being (SFWB), relationship with the doctor (RWD), emotional well- being (EWB) and functional well-being (FWB)- reflecting the multidimensional aspects of HRQL (41). The 20-item anaemia supplement consists of 13 questions that deal specifically with fatigue and 7 non-fatigue items.

In the HRQL study, the recommended scoring guidelines used were based on the *FACT-G* version 3(42). The *FACT-G* instrument was used in all data analyses.

D. Instruments: Questionnaire-Specific Background Information

1. Biodemographics

The biodemographics form allowed for systematic recording of patient information: dates of follow-up, cycle number for course of chemotherapy, type of chemotherapy received and bloodwork. Bloodwork consisted of hemoglobin levels, white blood cell, platelet, lymphocyte and neutrophil counts, as well as sodium, potassium and magnesium ion concentrations.

2. *Functional Assessment of Cancer Therapy(FACT)* Measurement System Questionnaires

The *Functional Assessment of Cancer Therapy (FACT)* measurement system is a family of instruments that use self-report to assess HRQL for patients with cancer and other chronic illnesses (42).

In the current study the *FACT-An* questionnaire was administered to the patients and data from the *FACT-G*, the core instrument of the *FACT-An*, was analysed (Appendix C). Development of the *FACT-G*, took place in three phases: item generation, item reduction, and scale construction.

D2i. *FACT-General* Questionnaire Development

a. *FACT-General* Item Generation

In the initial phase *of FACT-General (FACT-G)* item generation, a comprehensive list of candidate items were generated that would be systematically reduced. Items were generated from input given by patients and oncology caregivers.

Semi-structured interviews collected data from 45 patients [(n=15), lung (n=15), and colorectal (n=15)]. The average age of the sample was 60 years (range 27-76 years). Patient eligibility criteria were a minimum age of 18 years, the ability to read and speak English, receipt of treatment (including hormone therapy) for advanced stage (Stage III and IV) cancer and absence of brain metastases, delirium, psychosis or severe depression (41).

Demographic and treatment information were collected as well as the following questionnaires. A brief version of the *Profile of Mood States (Brief-POMS)* (41, 43) *Functional Living Index-Cancer (FLIC)* (15) and *Quality of Life Index (QLI)* (44) were administered. In addition, patients were asked about physical, emotional, family and social functioning and were required to create lists of HRQL items relating to their specific disease and treatment regimens.

In addition, 15 oncology specialists (8 physicians, 7 nurses) were also given the *FLIC* and *QLI* instruments to review. The panel was asked to prioritize the items based on specific cancer site and add any disease or treatment specific items. This data was pooled with that of the patient sample and all items were tabulated and rated independently for overlap and relevance to HRQL. An initial pool of 137 potential items for breast cancer patients, 126 for patients with colorectal cancer, and 107 for patients with lung cancer was generated (41).

b. *FACT-General* Item Reduction

The process of item reduction involved a new sample of patients rating the items on the previously generated list. There were 90 patients, [lung cancer (n=30), breast

cancer (n=30), colorectal cancer (n=30)], in this sample who underwent chemotherapy at the time of participation.

Patients evaluated the items for relative importance while undergoing treatment. The items were evaluated by ranking them on a 4-point Likert scale: 1=of little importance, 2=somewhat important, 3=very important, 4=extremely important. Items rated very important and extremely important were retained. Generally, these were similar across all disease sites.

c. *FACT-General* Formatting

The final candidate items were formatted and worded for compatibility with a 5-point Likert-type scale. For clarity and ease of completion, items were statements in the present tense, either positively or negatively phrased and with avoidance of double negatives. After reviews for redundancy and content, these 38-items constituted the *FACT-G*, version 1 (41). At present, there are four versions of the *FACT-G* questionnaire: version 1, version 2, version 3 and version 4 (41, 42).

D2ii. Psychometrics of *FACT* Instruments

a. *FACT-General* Questionnaire

1. Patient Sample

The 38-item *FACT-G* questionnaire version 1 was evaluated psychometrically by administering it to a third, previously untested, sample of cancer patients. Patients were accrued from four different sites: primary care centers as inpatients (n=121), primary care centers as outpatients receiving adjuvant therapy (n=195), free-standing non-profit

community support centers where various services were received (n=139) and from a pool of inpatients and outpatients (n=90) accrued to a concurrent quality of life study at Northwestern University, Chicago Illinois.

The heterogeneous cohort (n=630) consisted of 39% (n=246) breast, 15% (n=95) lung, 12% (n=75) colorectal, 8% (n=50) leukemia and lymphoma, 8% (n=50) head and neck, 6% (n=38) prostate, 2% (n=13) ovarian and 10% (n=63) other and unknown primary sites of disease. Patients with documented metastases of the central nervous system or overt clinical symptoms of psychopathology were excluded(41). Of the total cohort (n=630), 545(87%) cases provided assessable data (41).

2. Item Analysis and Factor Analysis

The psychometric evaluation process was divided into two phases: item analysis and factor analysis. In the first phase, the responses of the entire sample (n=545) were analysed for their fit to the concept of HRQL.

Using the procedure described by Wright and Linacre(45), patients' scores on each question were evaluated for their consistency with other responses. The Rasch Model of rating scale analysis was used to examine the properties of the resulting scale. Ten items, covering the areas of hope and spirituality were discarded due to poor fit. This left 28-items comprising the *FACT-G*; these items were subjected to factor analysis(41).

All questions were placed into six categories (or factors) reflecting collections of items and correlation coefficients indicated the association between each factor and a given item. At completion, five domains were created: physical well-being (factor 1),

social well-being (factor 2), emotional well-being (factor 3), functional well-being (factor 4 and 6), and relationship with doctor (factor 5). This formed the basis of *FACT-G,* version 2 (Table 1) (41).

Descriptive statistics were also available based on a sample of lung cancer patients, exclusively, evaluated using the *FACT-Lung (FACT-L).* The *FACT-L* is composed of the *FACT-G* and a 16-item lung cancer subscale. Data reported in Table 2 are from validity testing of the *FACT-L* instrument(46).

Table 1: *FACT-General (FACT-G)* Descriptive Statistics (n=466 mixed cancer patients)

Subscale	Number of items	Theoretical Range	Mean	Standard Deviation	Internal Consistency (α)	Percent of Variance
Physical Well-Being (PWB)	7	0-28	20.4	5.45	0.82	22
Social Well-Being (SWB)	7	0-28	21.9	4.77	0.69	9
Emotional Well-Being (EWB)	5	0-20	14.8	3.88	0.74	6
Functional Well-Being (FWB)	7	0-28	17.9	6.10	0.80	9
Relationship with Doctor (RWD)	2	0-8	6.85	1.51	0.65	5
Total	28	0-112	82.0	15.8	0.89	51

Source: Cella et al. J Clin Oncol 11(3) 1993: 570-579

Table 2: Descriptive Statistics for *Functional Assessment of Cancer Therapy-Lung (FACT-L)* Scales and Item Totals in a Lung Cancer Population (n=116)

***FACT* Instruments (number of items)**	**Mean**	**Standard Deviation**	**Internal Consistency (α)**
FACT-General (FACT-G) (28)	84.1	14.1	0.87
Physical Well-Being (PWB) (7)	20.7	5.0	0.75
Social Well-Being (SWB) (7)	23.2	3.9	0.56
Relationship with Doctor (RWD) (2)	7.2	1.0	0.40
Emotional Well-Being (EWB) (5)	15.5	3.7	0.69
Functional Well-Being (FWB) (7)	17.4	6.2	0.80

Source: Cella et al. Lung Cancer 12(2) 1995: 199-220

3. Questionnaire Validation

Validity testing was conducted on only those patients accrued in a primary care setting (n=316). These individuals were administered a battery of instruments which included the *FLIC,* a shortened form of *Profile of Mood States (Brief-POMS), Taylor Manifest Anxiety Scale (TMAS), ECOG* and the *Marlowe-Crowne Desirability Scale (M-CSDS)* (Table 3).

Table 3: Pearson Correlations Across Measures in Validation Packet for *FACT-General (FACT-G)* in a sample of heterogeneous cancer patients (n=316)

Scale	*Functional Life Index-Cancer (FLIC)*	*Brief-Profile of Mood States (B-POMS)*	*Taylor Manifest Anxiety Scale (TMA)*	*Eastern Co-operative Oncology Group Performance Status Rating (ECOG PS)*	*Marlowe-Crowne Desirability Scale (M-CSDS)*
FACT-General (FACT-G)	0.79	-0.68	-0.58	-0.52	0.22
FLIC		-0.66	-0.58	-0.60	-0.16
B-POMS			0.47	-0.46	-0.18
TMA				0.32	-0.19
ECOG PS					-0.06

Source: Cella et al. J Clin Oncol 11 (3) 1993: 570-579

Construct validity (the extent to which the tool measures what it purports to measure) was examined by measuring the instrument for convergent and divergent validity. Convergent validity was evaluated by comparing *FACT-G* scores and those of similar instruments, *Brief-POMS, ECOG*, *FLIC, TMAS* completed at the same time.

The *Profile of Mood States (POMS)* is a widely used 65-item self-report consisting of scales of subjective mood states. The *Brief-POMS* is an abbreviated 37-item (rated on a 5-point scale rate from 1=not at all to 5= extremely) short form of this instrument demonstrating good internal consistency (α=0.92) and test-retest reliability (r=0.95)(43).

The *Eastern Co-operative Oncology Group (ECOG)* scale is a 5-point performance status measure. It will be described in further detail in Section D3.

The *Functional Life Index-Cancer (FLIC)* is tool made up of a total of 22-ietms where each question consists of a 7 point visual analogue scale. The self-administered questionnaire (15) represents a validated measure of the overall functional qualities of a cancer patient's day-to-day life. The tool has demonstrated good internal consistency (α=0.91) and high test-retest reliability (r=0.74) in psychometric testing.

These instruments comprehensively covered domains paralleled in the *FACT-G,* and therefore, high correlations were expected. Cella et al.(41) do not define standards for interpreting association. However higher coefficients, specifically those having an absolute value over 0.55, are consistently referred to as strong associations, absolute values less than or equal to 0.55 but above 0.22 are referred to as moderately high, and weakly correlated are those with an absolute value less than or equal to 0.22. The results of convergent validity testing showed Pearson's correlations with *FLIC* was r=0.79 and correlations with the measures of mood distress *TMAS* and *POMS were* r=-0.58 and r=-0.65, respectively. The correlation with *ECOG* was moderately high but still within the expected range (r=0.56)(41).

Divergent validity was evaluated by examining the association between *FACT-G* scores and dissimilar measures (*M-CSDS).* Given reasoning that parallels convergent validity, low correlations were expected from this comparison. The correlation supporting divergent validity, evaluated by the social desirability scale of *M-CSDS,* was low (r=0.22)(41).

FACT-G construct validity was also assessed in a separate study evaluating the psychometric properties of the *FACT-L* (Table 4). These results are noteworthy as the

FACT-L instrument was evaluated on a sample of lung cancer patients (n=116), only (46).

Psychometric evaluations were also carried out to examine *FACT-G* test-retest reliability and responsiveness to change (41). Regarding test-retest reliability, *FACT-G* was administered to a previously untested sample of 70 patients with mixed cancer diagnoses with a second administration within 3 to 7 days. Of the sample accrued, 60 patients completed the administration within the given time period and test-retest reliability is based on these patients' results. Test-retest coefficients (type of correlation used was not specified) were as follows: physical well-being (r=0.88), social well-being (r=0.84), emotional well-being (r=0.82), relationship with doctor (r=0.83) and global score (r= 0.92) (41).

Table 4: Pearson's Correlations Across Measures in Validation Packet for *FACT-Lung* (*FACT-L*) in a sample of lung cancer patients (n=116)

Scale	*Brief POMS*	*FLIC*	PWB	SWB	RWD	EWB	FWB	*FACT-G*	*FACT-L*	*M-CSDS*
ECOG	0.29	-0.59	-0.54	-0.13	-0.07	-0.27	-0.41	-0.43	-0.47	-0.05
Brief-POMS		-0.57	-0.28	-0.25	-0.08	-0.51	-0.43	-0.45	-0.44	-0.02
FLIC			0.57	0.28	0.11	0.48	0.52	0.58	0.60	0.06
PWB				0.24	0.13	0.36	0.60	0.52	0.60	0.12
SWB					0.49	0.45	0.45	0.51	0.51	-0.07
RWD						0.24	0.21	0.33	0.33	0.05
EWB							0.51	0.55	0.53	-0.09
FWB								0.66	0.66	-0.01
FACT-G									0.66	-0.08
FACT-L										-0.07

Source: Cella et al. Lung Cancer 12 1995: 199-220

ECOG: Eastern Co-operative Oncology Group Performance Status Rating

Brief-POMS: Brief Profile of Mood States

PWB: Physical Well-Being

SWB: Social Well-Being

RWD: Relationship with Doctor

EWB: Emotional Well-Being

FWB: Functional Well-Being

FACT-G: FACT-General

FACT-L: FACT-Lung

M-CSDS: Marlowe-Crowne Social Desirability Scale

4.Sensitivity to Change

Sensitivity to change was also measured in the questionnaire validation process. Known clinical change in patient groups over time was compared to changes reflected in the instrument score over time. To investigate this property in the *FACT-G*, *ECOG* was used as an indicator of change in health status. That is, change in *ECOG* was expected to parallel corresponding changes in the physical and functional domains of the *FACT* instrument.

The *FACT-G* was administered to a previously untested sample of 104 patients currently receiving chemotherapy for advanced breast, lung, or colon cancer. A second administration occurred 2 months later. Patients were then categorized into three groups according to change in *ECOG* score over time: decline in *ECOG* (n=127); improvement in *ECOG* (n=17) and unchanged (n=60)(41).

Univariate testing showed the physical domain (F= 12.6) and the functional domain (F= 5.1) were best able to register change. This level of responsiveness was qualitatively greater than other subscales; social well-being (F= 2.6), emotional (F= 3.9), Relationship with Doctor (F= 0.4). Furthermore, multivariate analyses of variance confirmed that the physical ($p<0.001$) and functional ($p<0.01$) domains were statistically the strongest contributors to sensitivity measurement. Statistical sensitivity to change was also reflected in the emotional subscale ($p<0.05$) but not the social or relationship with doctor subscales ($p>0.05$)(41).

5. Weaknesses in the Instrument

There are several limitations in the *FACT-G*. First, given that *FACT-G* is a general cancer assessment measure, the *FACT-G* documents a broad range of items, including those that are more important in some pathologies but are of lesser importance in others. Consequently, certain disease or treatment-specific items may be omitted(41).

Second is the presence of floor effects (47). The inability of an instrument to distinguish deterioration of patient HRQL beyond a specific value may compromise instrument responsiveness. Given the generic nature of disease assessment, the *FACT-G* may not be able to capture effectively change in subjects who start with poor HRQL and continue to deteriorate (47).

D2b. *FACT-Anaemia(FACT-An)* Questionnaire

1. Background

In this study, the *FACT-An* instrument was administered to patients. The *FACT-An* consists of the *FACT-G* core questionnaire (34 items) and a 20-item anaemia supplement. The anaemia supplement consists of 13 items dealing with fatigue and 7 non-fatigue items (Table 5).

Table 5: Descriptive Statistics for *Functional Assessment of Cancer Therapy (FACT)* Instruments in a Heterogeneous Cancer Population

FACT Instruments (Number of Items)	Subscale Means (n=49)*	Standard Deviations (n=49)*	Subscale Range (n=49)*	Initial/ Retest**	Test-Retest Correlations (n=44)***
***FACT-General (FACT-G)* (28)**	84.9	14.8	48-111	0.88/0.90	0.82
***FACT-Fatigue (FACT-F)* (41)**	121.7	23.1	59-163	0.95/0.95	0.87
***FACT-Anaemia (FACT-An)* (48)**	141.5	26.7	67-190	0.96/0.96	0.87

Source: Yellen et al. J Pain Sympt Manag 13(2) 1997: 63-97

* n based on initial administration
** n for internal consistency analyses vary as a function of missing data within each scale
*** n based on re-test administration. Method of evaluation not specified.

2. Convergent-Divergent Validity

Yellen et al.(48) evaluated the instrument's psychometrics on a heterogeneous patient sample (n=50) by administering a battery of questionnaires that included the *FACT-An*, *ECOG*, the *Piper Fatigue Scale(PFS)*, the Fatigue and Vigor sub-scales of the *POMS,* and a short-form of the *Marlowe-Crowne Social Desirability Scale(MCSDS).* Socio-demographic, disease, and treatment information were also gathered.

Given Yellen et al.(48) has not defined standards for interpreting association, the following scheme by Guyatt et al.(49) is adopted. Strong correlations are >0.50, moderate are 0.3 to 0.50, weak are 0.20 to 0.34 and negligible or not correlated are 0.00 to 0.19. These standards will be used consistently throughout this paper unless otherwise stated.

The *Piper Fatigue Scale* assesses subjective fatigue using responses to a 46-item visual analogue scale. In validation studies, this instrument was reported to have good internal consistency (α= 0.85)(50).

The Vigor and Fatigue subscales of the *POMS* have demonstrated good internal consistency (α= 0.89 and α= 0.94, respectively) and high test-retest reliability (r=0.65) over an average 20-day period. The instrument has also shown to have good construct validity in multiple empirical investigations (43).

The *Marlowe-Crowne Desirability Scale- Short (MC-1)* form is a ten-item measure of conformity with socially desirable traits(51). This is an indirect measure of a person's need for social acceptance. The *MC-1* was added for evidence for divergent validity. The lengthier parent version demonstrates good internal consistency (α=0.66-0.70) and is significantly correlated with the longer form (r=0.80-0.90).

The validation of the *FACT-An* involved administration of 49 baseline assessments and 44 retest administrations of the *FACT-An*. Initially, patients completed the validation packet and upon retest, 3- 7 days later, completed only the *FACT-An*.

The *FACT-An* has strong convergent validity with instruments that are associated either with fatigue or anaemia (Table 6). Psychometric testing using Pearson's coefficient showed this instrument had good correlation with *POMS Fatigue* (r=-0.77), *POMS Vigor* (r=0.65) and *Piper Fatigue* (r=-0.75). In addition, *FACT-An* proved unrelated to social desirability (r=0.04), the short form of the *MCSDS*(48).

Yellen et al.(48) also examined the anaemia supplement breaking it down into a 13-item fatigue and a 7-item non-fatigue subsections, for convergent and divergent validity. The 13 fatigue items had strong correlations with *POMS Fatigue* (r=-0.83),

POMS Vigor (r=0.61) and *Piper Fatigue* scales (r=-0.58). There was limited correlation with *MC-1* (r=-0.18). In the 7 non-fatigue items, the scored strongly with the *POMS Fatigue* scale (r=-0.77), the *POMS Vigor* (r=0.52) and *Piper Fatigue* (r=-0.57) scales. A relationship was not found between the fatigue items of the anaemia subscale and the *MC-1* (r=-0.11)(48).

Table 6: Convergent/Divergent Validity of the *Functional Assessment of Cancer Therapy (FACT)* Scales and Subscales in a heterogenous cancer population (n=49)

Scale (Number of Items)	*FACT-Fatigue (FACT-F) (41)*	*FACT-Anaemia (FACT-An) (48)*	*FACT-General (FACT-G) (28)*	*Fatigue subscale (13)*	*Non-fatigue items (7)*	*POMSFatigue (7)*	*POMS-Vigor (8)*	*Piper-Fatigue (41)*
Fatigue subscale	0.66	0.73	0.66					
Non-fatigue items	0.79	0.79	0.68	0.77				
POMS-Fatigue	-0.74	-0.77	-0.57	-0.83	-0.77			
POMS – Vigor	0.66	0.65	0.59	0.61	0.52	-0.52		
Piper-Fatigue	-0.75	-0.75	-0.58	-0.77	-0.57	0.75	-0.43	
Marlowe-Crowne	0.04	-0.06	0.10	-0.07	0.18	-0.11	0.15	0.23

Source: Yellen et al. J Pain and Sympt Manag 13(2) 1997: 63-74

3. Criterion Validity: Hemoglobin and Performance Status

Administering the questionnaire to patients with varying degrees of anaemia evaluated the discriminative properties of the *FACT-An*. The patient cohort was divided into groups of high (>13.0 g/dL), moderate (11.0-12.9 g/dL) and low (<11.0 g/dL) hemoglobin levels. Each of these groups was associated with deteriorating HRQL and group membership was to be predicted by *FACT-An* (48).

Psychometric analysis found hemoglobin levels were statistically significant in their association with HRQL scores as measured by the *FACT-An* instrument (p= 0.013). Post-hoc comparisons of groups using the Tukey test indicated that the effect was greatest in differentiating the very low hemoglobin group (<11g/dL) from the highest group (>13 g/dL) (p= 0.01). As well, the 13-item Fatigue subscale was successful in discriminating between low (p= 0.16) and high mean hemoglobin levels (p= 0.041). Post-hoc comparisons of the groups via the Tukey test revealed that the 7 non-fatigue items discriminated between all three groups with varying levels of significance (low p=0.016, medium p=0.005, high p=0.05)(48).

Discriminant validity was also evaluated using the *ECOG* performance status measure. All specific sub-scales and total scores discriminated levels of performance status in a sample divided into three levels (*ECOG*=0 versus 1 versus 2,3). Higher performance status was expected to be associated with higher HRQL scores and that *FACT-An* scales would predict group membership. Post-hoc comparisons suggested all subscales and total scores successfully discriminated: *ECOG*= 0 versus *ECOG*= 2 and *ECOG*= 3 (p= 0.003 to 0.039) and *ECOG*= 1 versus 2,3 (p=0.003 to 0.039)(48).

3. *Eastern Cooperative Oncology Group(ECOG)* Performance Status Rating

Performance status is a global assessment of the patient's level of function and ability in self-care. Performance status is a major prognostic factor of survival time, a predictor of the benefit and toxicity of treatment, of co-morbidity and other 'host factors'(52). There are two widely used measures of performance status in cancer:

Eastern Co-operative Oncology Group(ECOG) Performance Status Rating and *Karnofsky's Performance Status Assessment(KPS).*

ECOG is a single item measure, rating a patient's ability to participate in daily activities without the need for rest (Appendix D). Developed from a set of standardised performance criteria (53), *ECOG* score is a 5-point scale ranging from 0 ("I have normal activity without symptoms") to 4 ("I am unable to get out of bed"). A worsening performance status (higher score) is associated with increased involvement of distant metastatic sites, an increased tumour burden and decreased survival (10, 54).

Limited information was found on the psychometrics of the *ECOG* scale. Inter-rater reliability indicated a significantly high correlation was observed among physician raters ($r=0.75$). Results also showed *ECOG* produced a strong correlation ($r=0.64$) between physician and patient self-evaluations of their disease ($p<0.05$).

E. PROGNOSTIC CLINICAL VARIABLES

Seven clinical and demographic variables, (age, sex, histology, previous weight loss, presence of liver metastases and *ECOG* performance status), studied extensively in the literature, were chosen as possible clinical covariates (55-58). The relevance of each as a prognostic indicator in lung cancer is outlined below. To examine the simultaneous effect of multiple variables, these potential confounders were entered into the multivariate models for each hypothesis.

1. Performance Status Rating

Performance status is a frequent indicator of co-morbidity and is a prognostic indicator for survival (57). Measuring the impact of disease has confirmed significant correlations between performance status and loss of function (17, 59), and physiologic (11, 60) and psychological distress (33, 34, 61, 62).

Multiple therapeutic clinical trials have confirmed its value as a good predictor of baseline HRQL and as such, it is often used as a proxy for baseline HRQL in studies of cancer patients (63). The number and severity of patients' symptoms increase with worsening performance status (64). Bergman et al.(65) reported that poor performance status along with the symptom constellation of dyspnea, cough and pain are indicative of advanced disease and worsening prognosis. In addition, specific symptoms like anxiety, fatigue, malaise, dyspnea and pain are often present at diagnosis in both SCLC and NSCLC cases, progressing with a decline in functional status (26)

Pain is consistently a prominent symptom for many patients with advanced lung cancer (27), affecting physical function (performance status) both directly and indirectly. Symptom palliation can be essential to facilitating both physical and emotional well-being(66).

Disruptions in a patient's capacity to engage in a variety of physical activities are common with disease progression. Physical compromise is often followed by subsequent emotional decline (43, 66, 67) and deteriorating psychological wellness, manifested by increasing levels of anxiety and depression (62, 68). In addition, psychiatric disorder in lung cancer patients is significantly associated with poorer performance status (69).

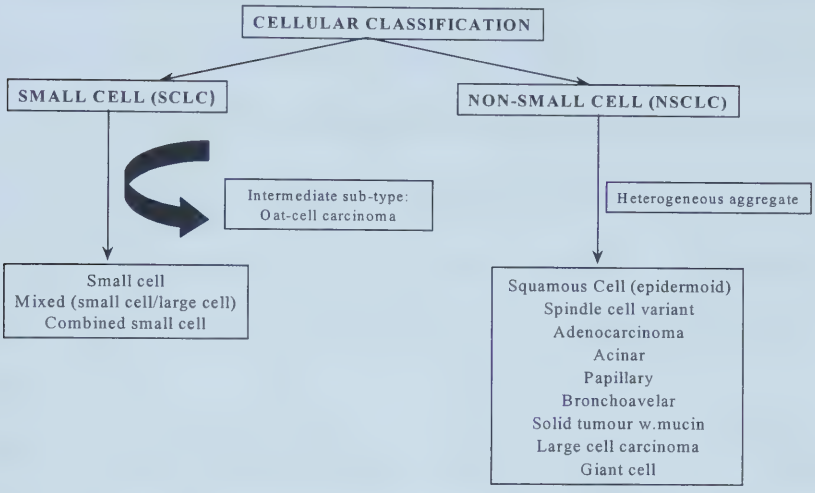
In the HRQL study, *ECOG* performance status was entered into the statistical models as a trichotomised variable (*ECOG* 0= group 1, *ECOG* 1= group 2 and *ECOG* 2+ = group 3). *ECOG* 0 indicates full activity and the ability to carry on all pre-disease performance without restriction. *ECOG* 1 indicates that the individual has symptoms of disease but is ambulatory and able to carry out activities of daily living. Patients in categories 2 and above all show marked symptoms of disease progression and as such were grouped together.

2. Histology

Four major cell types comprise the histological classification of 95% of all primary lung neoplasms: these are epidermoid, small cell, adenocarcinoma and large cell carcinoma(10, 70). These categories can be dichotomised into small cell lung cancer (SCLC) with small cell histologies only, and non-small cell (NSCLC), comprising the remaining cell types (Figure 4).

Each cell type has different natural histories and responses to therapy. Treatment decisions are made on the basis of distinctions between histological classification of a tumour as a small cell carcinoma or one of the non-small cell varieties(70).

Figure 4: Histo-Pathology of Lung Carcinoma



Source: Cagle PT, Tumors of the Lung,1995

i. Non-small Cell Lung Cancer (NSCLC)

The non-small cell (NSCLC) histology, representing approximately 70%-80% of all lung cancer cases, are a heterogeneous aggregate of at least 3 distinct cell types including squamous carcinoma, adenocarcinoma and large cell carcinoma (70, 71)

In advanced stage disease, radiation therapy can offer palliation to the majority of patients from the localised tumour mass (72) and chemotherapy can produce short-term improvement in disease-related symptoms (73, 74). However given response rates are 20-40%, these treatments offer only modest improvements in median survival(75). In addition, overall 5-year survival remains poor (76) with 5-10% of Stage III patients surviving and 2-5% of Stage IV patients surviving.

ii. Small Cell Lung Cancer(SCLC)

Small cell (SCLC) histologies represent approximately 20-30% of all lung cancer cases (70). Compared with other cell types, SCLC has a greater tendency to be widely disseminated and patients typically develop distant metastases (Stage IV) by the time of diagnosis (77). Combination chemotherapy plus chest irradiation does not appear to improve survival compared with chemotherapy alone in extensive stage SCLC. However, radiation therapy can play an important role in palliation of symptoms of the primary tumour and metastatic disease, particularly brain, epidural, and bone metastases(78).

Without treatment, SCLC has the most aggressive clinical course of any type of pulmonary tumour with a median survival time of only 2 to 4 months from date of diagnosis(10, 77). However, even in advanced stages, SCLC is more responsive to chemotherapy and irradiation than NSCLC (58, 78) and response rates of 65%-90% can be achieved (77). As a result, there can be a 4-5 fold improvement in median survival compared with patients receiving no therapy(78). However, the risk of mortality still is high; the overall survival at 5-years is 5% to 10% (58, 79).

3. Clinical Stage

Lung cancer staging is primarily established by the location of the tumour (anatomic staging)(10, 80). Anatomic stage of disease is based on a combination of clinical (physical examination, radiologic and laboratory studies) and pathologic examination (biopsy of lymph nodes, bronchoscopy, mediastinoscopy or anterior mediastinotomy)(81, 82).

Determination of stage is an initial diagnostic evaluation to define location and extent of primary and metastatic tumour involvement. The UICC/AJCC has designated staging by TNM classification for lung cancer (Table 7)(Appendix E)(83).

Table 7: American Joint Committee on Cancer/ Union International Contre le Cancer (AJCC/UICC) Staging for Lung Cancer

Stage	TNM
I	T1, N0, M0 or T2, N0, M0
II	T1, N1, M0 or T2, N1, M0 or T3, N0, M0
IIIA	T1, N2, M0 or T2, N2, M0 or T3, N1, M0 or T3, N2, M0
IIIB	Any T, N3, M0 T4, Any N, M0
IV	Any T, any N, any M1

Source: AJCC, AJCC Staging Manual, 1997:127-137

T: Primary Tumour

N: Regional Lymph Nodes

M: Distant Metastases

1-4: Depth of tumour invasion

i. Stage I and II NSCLC

At diagnosis, patients with NSCLC can be trichotomised into staging groups that reflect the extent of disease (pathological stage) and the resultant treatment approach.

The first group of patients has tumours that are of limited stage (Stage I and II) without nodal or metastatic involvement and are surgically resectable. Individuals presenting with early staged disease have the best prognosis with 5-year survival rate of 60% (71, 84).

ii. Stage IIIa, IIIb and IV NSCLC

The second group includes patients with either locally (T3-T4) or regionally (N2-N3) advanced lung cancer who have a diverse natural history. This group is treated with radiation therapy or more commonly, with radiation therapy in combination with chemotherapy or other therapy modalities. Selected patients (T3 or N2) can be treated effectively with surgical resection alone(81, 85).

The group of patients with distant metastases (M1) at the time of diagnosis can be treated with radiation therapy or chemotherapy for palliation of symptoms from the primary tumour. Patients with good performance status, women and patients with distant metastases confined to a single tumour site appear to live longer than others. Cisplatin-based chemotherapy has been associated with short-term palliation of symptoms and a small survival advantage (72, 86, 87).

iii. Stage I and II SCLC

At diagnosis, approximately 30% of patients with Stage I or II small cell carcinoma will have tumours confined to the hemithorax of origin, the mediastinum or the ipsilateral supraclavicular nodes. A median survival of 16 to 24 months can be expected and most 2-year disease-free survivors come from this group. A small proportion of patients with early stage disease may benefit from surgery with adjuvant chemotherapy; these patients have an even better prognosis(10, 88). Combination chemotherapy yields a short-term response in 65% to 90% of the population and complete response in 45% to 75% of cases diagnosed. However, the presence of occult metastatic disease is common to patients with limited stage SCLC(88).

Mature results of prospective randomised trials suggest combined modality therapy in early stage SCLC produces a modest but significant improvements in survival compared to chemotherapy alone (88-90). Two meta-analyses (91, 92) reported an approximate 5% improvement in 3-year survival rates relative to those receiving chemotherapy alone. Chemotherapy with concurrent chest radiation therapy has been used in multiple single institutional studies and in cooperative group studies. These studies have consistently achieved median survivals of 18 to 24 months and 40% to 50% 2-years survival with less than 3% treatment-related mortality. Most of the benefit occurred in patients less than 65 years.

The optimal duration of chemotherapy for patients with limited stage SCLC is not clearly defined but there is no improvement in survival after the duration of the drug exceeds 3 to 6 months. There is no evidence from randomised trials that maintenance of chemotherapy prolongs survival for patients with limited stage SCLC (29, 78, 93).

iv. Stage IIIa, IIIb and IV SCLC

Extensive stage (Stage IIIa, IIIb or IV) SCLC means tumour spread is beyond the limitations defined in early stage disease(10, 94). These patients have a worse prognosis than patients with limited stage disease and a median survival of 6 to 12 months is reported with current therapies (95).

Patients with distant metastases (M1) are always considered to have extensive stage disease. As in limited stage SCLC, chemotherapy should be given as multiple agents in order to produce the best results. Dose and schedules used in current programs yield limited responses in 70% to 85% of the population and complete response rates in

20% to 30% of the extensive disease population. Since overt disseminated disease is present, combination chemotherapy is the cornerstone of treatment of this advanced stage SCLC (29, 96). Treatment goals are predominantly palliative as long-term survival is rare.

4. Sex

The evidence on the role of sex as an independent prognostic indicator of patient survival time is mixed. Multiple analyses have been unable to note any survival advantage for women with NSCLC or SCLC (97-99). A large evaluation of prognostic factors of 3873 patients from ten centers in Britain failed to identify sex as a major prognostic factor (100) and Idhe et al.(89) of the National Cancer Institute, U.S., found female patients achieved no superior survival relative to men. This analysis, however, was based on a sample of 106 patients of which only 16 were female.

However, the literature also strongly supports findings showing a patient's sex is an essentially relevant predictor of survival (55, 56, 101, 102). The advantage of female patients over males was more pronounced in subgroups of cases with additional favourable prognostic features than in patients with adverse characteristics. Four variables- sex, extent of disease, performance status and history of smoking- are consistently reported as statistically significant prognostic factors, whereas age and weight loss prior to chemotherapy have been found to be less important(95). Furthermore, analyses have indicated that the factors sex, performance status and history of smoking are strongly predictive of survival. This impact was only surpassed by the influence of extent of disease on prognosis(95).

The prognostic value of sex appears to be especially important for long-term survival. The Cancer and Leukemia Group B(CALGB) reported 35% of female patients with limited stage lung cancer achieved a 2-year survival time compared to only 15% of male patients(103). Parallel results were found in a study by Wolf et al.(95) who found that of 114 females with SCLC, 35% of these patients achieved complete remission, and a median survival time of 12.1 months. As well, 2-year survival was achieved by 19% of the sample. On the other hand, the complete remission rate of the 652 male patients was 25%, median survival was 9.8 months, and a 2-year survival was reached by 8% of the sample. This difference in survival time between the sexes was statistically significant ($p=0.0002$). These findings were exclusive to limited stage. No differences in prognoses were reported in extensive stage disease.

5. Age

The covariate of age has been repeatedly investigated for its role as an independent prognostic indicator of survival for patients with lung cancer. Results from these studies are mixed, however, as younger (less than 40 and less than 60 years) (104) and older ages (greater than 60(101) and greater than 70 (56)) are reportedly associated with unfavourable survival.

Age, like sex, has been found to be most significant when linked with other prognostic factors, specifically performance status and histology. Favourable performance status (*ECOG* 0 or 1) appears to be significantly more common in patients aged less than 60 years, (89, 103) compared to the very elderly (over 80 years)(103, 105).

With respect to histology, in a meta-analysis, Wolf et al.(95) reported that age greater than 60 years is a weak survival predictor in NSCLC as a univariate (10 positive analyses out of 23) and its value disappears completely in multivariate models (only 4 positive studies out of 23). In SCLC, age may be a more predictive (5 studies out of 8 studies) covariate even though, in younger cohorts, a lower percentage (range 3-35%, median 18%) of patients present with this histology (104, 105). The frequency of SCLC is higher in older patients (above 50 years) in comparative studies, ranging from 12% to 37%, with a median of 30%(104).

Given these published observations, as well as the age distributions in our cohort in the HRQL study, the age was entered into the Cox model as a trichotomised variable (age <57 years=0, age 57-64 years=1 and age ≥65 years=2) in all statistical analyses in order to reflect the potentially varying influence of chronological age on patient survival.

6. Hepatic Metastases

Multiple studies have confirmed that the presence of hepatic metastases is an independent prognostic factor of poor long-term survival in patients with lung carcinoma (56, 100, 106). Most recently, research by Tas et al.(60), Vigano et al.(59) and Naughton et al.(55) have reported statistical significance in analyses examining the association between presence of hepatic metastases and survival, contributing to an already well established area of literature.

The importance of liver metastases is linked with stage; extensive stage patients with liver involvement have significantly worse survival than limited stage patients and other extensive stage patients without liver involvement (54, 103). In addition, a trend

was reported whereby limited-stage patients live the longest (median= 14 months), followed by extensive stage patients without liver metastases (median= 11 months) and finally by those extensive stage patients with liver metastases (median= 7 months)($p<0.001$)(54).

7. Response to Treatment

The literature records that in the majority of studies, 'response to treatment' is analysed as a constellation of prognostic variables. Of these, histology, stage, and performance status reoccurs as the most predictive of patient response to course of therapy (3, 36).

O'Connell et al.(102), investigated response to treatment as a specific covariate, defining it as "the effect of a major response to chemotherapy on survival". A conditional analysis tracking survival time subsequent to the final day (day 70) of therapy was performed; the post-treatment variable of 'major objective response with chemotherapy' was added to the Cox model. Response to treatment was strongly associated survival as patients with positive responses had a median survival of 15.1 months after day 70 compared with 4.7 months after day 70 for patients with negative or no response.

Recent studies (107) have shown baseline HRQL has a greater impact than most known prognostic factors given that stable or improved HRQL depends mainly on tumour response. That is, baseline HRQL is not only a strong indicator of both response to the treatment and survival, it has also been found that physical and functional

dimensions of HRQL are strong predictors of tumour response in patients receiving chemotherapy.

Response to treatment, as defined by the *ECOG* study group (53), has classified patient outcome into five basic response categories: complete response, partial response, stable, progression and no evidence of disease.

i. Complete Response

A complete response is constituted by the components of clinical and pathologic response. A clinical response is defined as the complete disappearance of all clinically detectable malignant disease for at least 4 weeks. A pathologic response is constituted by pathologic proof of clinically complete response of known malignant disease. Both these criteria are requisites for a patient to be classified as having a complete response(53).

ii. Partial Response

A partial response has been defined by the *ECOG* group as a minimum 50% decrease in tumour area for at least 4 weeks without an increase in size of any area of known malignant disease of more than 25%, or appearance of any new areas of malignant disease. In a partial response, the area of primary tumour can be measured and classified into one of multiple categories: measurable and bidimensional, measurable and unidimensional or non-measurable(53).

Measurable and bidimensional change is a decrease of at least 50% in tumour area, or a 50% decrease in the sum of the products of the perpendicular diameters of multiple lesions in the same organ site for at least 4 weeks(53).

A measurable and unidimensional tumour change is a change greater than or equal to a 30% decrease in linear tumour measurement for at least 4 weeks. Potential tumour sites that should be evaluated in this category are mediastinal and hilar lymph nodes, palpable masses that can be measured in only one dimension and any malignant hepatomegaly(53).

A nonmeasurable, evaluable change in tumour mass is a definite improvement in evaluable malignant disease estimated to be in excess of 50%. Two independent investigators must agree upon this criterion and serial evaluations of chest x-rays should document this response for at least 4 weeks(53).

iii. Stable

'Stable' patient response to treatment is a lack of significant change in measurable or evaluable disease. This condition should be maintained for at least 4 weeks, or 12 weeks if bony metastases are present(53). Demonstrating this response patients should have no increase in size of any known malignant disease, no appearance of new areas of malignant disease, a decrease in malignant disease of less than 50%, a decrease in unidirectional measurable disease of less than 30% or increase in malignant disease of less than 25% in any site, and no deterioration in *ECOG* performance status of beyond 1, where elevation is related to malignant disease (53).

iv. Progression

Progression is a significant increase in size of lesions present at the start or after therapy or the appearance of new metastatic lesions not known to be present at the start of

treatment. It is also the presence of stable objective disease associated with deterioration in *ECOG* status of greater than 1, due to increasing malignancy (53).

The change in primary tumour site for disease progression can be: measurable, bidirectional and unidimensional, nonmeasurable and evaluable, nonmeasurable and nonevaluable or adjuvant(53).

Measurable, bidimensional and unidimensionable change in tumour sites have a minimum 25% increase in the area of any malignant lesions greater than 2cm or a similar increase in the sum of the individual lesions in a given organ site. Measurable, bidimensional and unidimensional change in tumour site can also include a minimal 25% increase in the size of the liver measurements or the appearance of new malignant lesions (53).

Non-measurable evaluable change is definite increase in the area of malignant lesions estimated to be greater than 25%, appearance of any new lesions or an increase in size or number of bony metastases.

Nonmeasurable, nonevaluable change is a definite evidence of newly clinically detectable (physical or radiographic) malignant disease. Adjuvant change is defined as definite clinical evidence of recurrent or metastatic malignant disease, proven via biopsy(53).

v. No Evidence of Disease

No evidence of disease is a lack of identifiable malignant disease in nonmeasurable, nonevaluable or adjuvant patients (53).

vi. Variable Manipulation

Response to treatment was obtained by data extraction from medical charts. For each case, diagnostic imaging reports were examined for a change in tumour burden subsequent to the clinical status at initial presentation. Histology was a factor in this evaluation: patients with SCLC typically respond well to chemotherapy initially and then plateau rapidly, while patients with NSCLC histology may respond slowly and show steady improvement with chemotherapeutic support. Given this, the number of radiology reports examined in order to determine response to treatment was specific to each case.

Given the small sample size of this study, the three 'responses to treatment' (increase in tumour burden, decrease in tumour burden or no change) were dichotomised into two groups: disease progression or no progression. Patients showing a decrease in tumour burden were included in the group 'no progression'. A new variable (progression) was created to represent change in tumour response and it was used in the statistical analysis of hypothesis S_1.

8. Previous Weight Loss

Multiple studies have documented that patient weight loss, both upon first presentation in the clinic and over the course of treatment, is prognostic of survival (57, 95). Vigano M et al.(59) investigated the statistical significance of weight loss greater 8.1kg in the 6 months preceding date of diagnosis. It was found the negative effects on survival from primary lung tumour are clinically and statistically different according to the amount of weight loss reported. That is, survival time clearly decreases in patients who had experienced greater weight loss. However, high weight loss has also repeatedly

been found as an important poor survival indicator only in cases with low lymphocyte counts and serum albumin levels of at least 3.5g/dL (95, 98, 102).

Weight loss accompanying progressive lung cancer and functional decline is also linked to patient depression, reportedly as due to metabolic cachexia (67, 68). It is commonly held that paraneoplastic syndromes are common in lung cancer patients. Systemic symptoms include anorexia, cachexia and weight loss and are seen in up to 30% of all cases(81, 94). However, other research has speculated this outcome may be the result of psychological distress, a manifestation of lack of eating due to depression(67).

F. Data Collection

1. Cohort Preparation

The Fatigue Study consisted of 43 records for 43 patients, which were entered into a spreadsheet, using the program Excel for Windows '97. After quality was assured, the information was transferred to the program SAS (version 8), for statistical analysis.

In 4(9.52%) patients, performance status was recorded as a *Karnofsky's Status* measurement. In these cases, conversion tables found in the literature were used to transfer the measure into an *ECOG* measurement(108).

Patients underwent differing chemotherapeutic doses, combinations and number of cycles depending on their histology, response to therapy, and tolerance of treatment toxicity. At baseline, 43 patients were enrolled in the study. As patients completed their course of treatment, a decreasing number remained in the study cohort.

2. Linkage to the Registry

Using the medical record number (ACB number), patients in the Fatigue Study cohort were matched to their respective electronic records in the Alberta Cancer Registry (ACR). The ACR is a province-wide database, maintained by the Division of Epidemiology, Prevention and Screening, that records cancer incidence for comparison within the province and between provinces.

Patients in the HRQL cohort were linked with their record in the ACR database by using identification numbers (medical record number) and disease information (topography codes c34.0-c34.9). Six (14.3%) patients presented with metachronous primaries. In these cases, the date of diagnosis (provided it was within the period of accrual) was used to link these patients with registry data. In the HRQL cohort, all 42 patients were linked with their record in the ACR.

In the study database, 106 variables were recorded. Of these, 83 variables were exclusive to the questionnaire battery, 20 were exclusive to the ACR, and 3 were extracted from both sites. In the situations of overlap, ACR data was used preferentially in order to minimise non-systematic error.

3. Errors influencing Data Entry and Linkage Processes

Data entry is prone to several common random errors: transcription or substitution errors (digits are incorrectly recorded because of misreading or miskeying), transposition errors (correct digits are entered in the wrong order) and shift errors (addition or omission of zeros)(109). In the HRQL Study, data was entered as part of an identifying system, therefore error rates were minimised by a digit check routine. In addition, data was

independently double-entered by two individuals. These sets were then subtracted to identify any errors.

The literature records multiple methods of imputing missing, illegible or ineligible data- trend imputation, mean imputation and ratio imputation (110). In our study, this problem was recorded in 7(16.7%) patient records. In those questionnaires where two responses were completed for the same question, the response indicative of higher HRQL was consistently entered. This method was chosen as the literature did not favour one specific method for data imputation. In situations where patient biodemographic data was missing, medical records were used for data extraction. Of the 43 patient records, 42 cases were analysed. One individual was ineligible for study given a change in treatment regimen and withdrawl of receipt of chemotherapy (a study inclusion criterion).

In the process of linkage, error can also occur. The main problem was an issue with blocking, the situation where truly linked variables disagree so that records are never brought together for comparison. To minimise the effects of blocking, multiple variables (ACB number, first name, last name and date of birth) were used to trace the same patient and as such, all patients (n=42) were linked.

4. Scoring the *FACT-G* Questionnaire

The *FACT-G* questionnaire was scored following the guidelines documented in the *Functional Assessment of Cancer Therapy Manual* (42) and with use of a program created on SAS software (version 8.12; SAS Institute, Cary NC). HRQL scores were calculated on the core instrument of the *FACT-An,* the *FACT-G* (Appendix F) (111).

The *FACT-G* instrument was scored by subscale, using the arithmetic sum of systems of equations. Specific items were reversed, (reversing the sign on the item from 4), before being added, to obtain subscale totals. Reversion of negatively stated items ensured that higher scores meant higher HRQL. Following this, all subscale items were summed for a sub-total (subscale score) and then the total score (sum of the individual domains). The patient's global HRQL is this final total (41).

According to the guidelines stated by Cella et al. subscale scores for missing items were prorated by multiplying the sum of the number of items in the subscale, then dividing this by the number of items answered (41).

5. Description of the HRQL Cohort

The HRQL study cohort is described in Tables 8 and 9. The cohort consisted of 19 women (45.2%) and 23 men (54.8%), ranging in age from 39 through 78 years. The mean age for women was 63.1 years and the mean age for men was slightly lower at 60.9 years.

Six (14%) patients were listed in the ACR database as having multiple primaries with a disease site other than lung. In these cases, only the tumour sites with thoracic primaries were examined. Nineteen (45.2%) presented with tumour in the upper lobe of the lung, 13 (n=30.0%) presented with generalised lung tumours and one (2.4%) patient presented with disease at each of the sites- trachea, main bronchus, middle lobe and lower lobe.

Patients presented with advanced stage carcinoma of the lung, specifically UICC/AJCC Stage IIIa (n=1 or 2.4%), Stage IIIb (n=8 or 19.0%) and Stage IV (n=33 or

78.6%). These groups were dichotomised to Stage III (n=9) and Stage IV (n=33). The predominant histology was adenocarcinoma (n=16 or 38.1%), although patients also presented with small cell 8 (19.0%), squamous cell 8 (19.0%), generalised carcinoma 3 (7.1%), malignant tumour cells 2 (4.8%) and 1 (2.4%) each of mixed cell type, kertinizing squamous cell and adenosquamous carcinoma. These histologic classifications were dichotomised; 34 (81.0%) patients had NSCLC and 8 (19.0%) had SCLC. It is noteworthy that these histologic proportions parallel those recorded in the literature (70).

Table 8: Bio-Demographic Characteristics of the HRQL Cohort (n=42)

Bio-Demographic Variables	Frequency (Percentage)
Gender	
Male	19 (45.2%)
Female	23 (54.8%)
Vital Status	
Alive (censored to March 31, 2001)	4 (9.5%)
Dead	38 (90.5%)
AJCC/ UICC Stage	
IIIa	1 (2.4%)
IIIb	8 (19.0%)
IV	33 (78.6%)
AJCC/UICC Stage dichotomised	
III	9 (21.4)
IV	33 (78.6%)
ECOG PSR	
0	10 (23.8%)
1	22 (52.4%)
2	8 (19.0%)
3	1 (2.4)
4	1 (2.4%)
ECOG PSR trichotomised	
0	10 (23.8%)
1	22 (52.4%)
≥2	10 (23.8%)
Weight Loss at Baseline (lbs)	
0	20 (47.6%)
2	1 (2.36%)
5	1
7	1
8	1
10	1
12	1
13	6 (14.29%)
15	1
18	4 (9.52%)
20	1

Bio-Demographic Variables	Frequency (Percentage)
25	1
30	1
40	2 (4.76%)
Weight Loss at Baseline (lbs) dichotomised	
≤10	25 (59.5%)
>11	17 (40.5%)
Histology	
Non-small cell (NSCLC)	34 (81.0%)
Small cell (SCLC)	8 (19.0%)
Morphology	
Tumour cell, malignant	2 (4.8%)
Carcinoma	3 (7.1%)
Large cell carcinoma	2 (4.8%)
Small cell carcinoma	8 (19.0%)
Small-large cell carcinoma	1 (2.4%)
Squamous cell carcinoma	8 (19.0%)
Squamous cell, kertinizing	1 (2.4%)
Adenocarcinoma	16 (38.1%)
Adenosquamous carcinoma	1 (2.4%)
Malignancy number	
1	36 (85.7%)
2	6 (14.3%)
Presence of Liver Metastases	
Present	28 (66.7%)
None	14 (33.3%)
Topography	
Trachea	1(2.4%)
Main bronchus	24.8%)
Upper lobe	19(45.2%)
Middle lobe,lung	1(2.4%)
Lower lobe, lung	5(11.9%)
Overlapping lesion of lung	1(2.4%)
Lung	13(30.0%)

Table 9: Descriptive Statistics for HRQL Cohort (n=42) at Baseline

Variables	Observations (n)	Mean	Standard Deviation	Median	Range observed
Age (years)	42	59.4	9.5	59.0	39.0- 78.0
Age Trichotomised (years)					
>57	15	49.8	5.8	52.0	39.0- 56.0
57-64	14	59.7	1.8	59.5	57.0- 63.0
65≤	13	70.4	4.4	68.0	65.0- 78.0
ECOG PSR	42	1.07	0.86	1.00	1.0- 4.0
***ECOG* Performance Status Trichotomised**					
0	10	0	0	0	-
1	22	1	0	1	-
2≤	10	2	2.3	2	2- 4
Baseline Weight Loss (lbs)	42	9.04	11.2	3.50	0- 40.0
Baseline Weight Loss Dichotomised (lbs)					
≤10	25	1.28	2.89	0.0	0- 10.0
>11	17	20.5	8.62	18.0	11.0- 40.0
Baseline *FACT-General (FACT-G)*	42	78.7	13.6	79.0	48.0- 107.0

VI. ANALYSIS

A. Primary Hypothesis (P_1)

The stratified Cox Proportional Hazards Model was used to examine the influence of baseline *FACT-G* on patient survival time (P_1). To examine the simultaneous effect of multiple variables, covariates sex, stage, histology, previous weight loss (dichotomised), presence of liver metastases and *ECOG* performance status (trichotomised) were entered into the survival model, stratified by trichotomised age. Appendix G illustrates the effect of each of these covariates on survival.

P-values were two-sided and were considered statistically significant at the 0.05 level; SAS software was used in all analyses. Overall survival time was measured until death due to any cause or to March 31, 2001. Survival curves were presented with the use of the Kaplan-Meier method.

1. The Stratified Cox Procedure

Cox regression can be used to account for the effects of continuous or discrete covariate measures (independent variable) when the dependent variable is 'time-until-event' data. The Cox Proportional Hazards Model can be written as(112):

$$h(Z, t_i) = h_0(t_i) \exp(\beta_1 Z_{i1} + \beta_2 Z_{i2} + , \ldots, + \beta_k Z_{ik})$$

In the Cox Model, k covariates on each of the subjects is measured, where i= 1,…,n subjects and $h_0(t_i)$ is the baseline hazard function for the ith subject. Here, the hazard function (h_z) is the conditional probability that patient death will occur at a time just larger than t_i (time at start of study) provided the subject has survived until time t_i.

This conditional probability is the instantaneous failure rate at time t_i and is written as the function $h(t_i)$. The hazard for the variable z_k is $e_{\beta k}$ (112).

Rearrangement of the general survival equation

$$[h(Z, t_i)/ h_0(t_i)] = \exp(\beta_1 Z_{i1} + \beta_2 Z_{i2} + , ..., + \beta_p Z_{ik})$$

shows that the exponentiated coefficient represents the hazard ratio or the ratio of the conditional probabilities of survival.

The stratified Cox model is a modification of the proportional hazards model, such that it allows for control by "stratification" of a predictor that does not satisfy the proportional hazards assumption (that the hazard ratio for a specific covariate remains constant over time)(112, 113).

The general stratified Cox model can be written as:

$$h_g(Z,t_i) = h_{0g}(t_i) \exp(B_1 Z_{i1} + B_2 Z_{i2} + ... + B_k Z_{ik})$$

This formula contains the subcript $g = 1, ..., j,$ indicating the gth stratum. The strata are defined as the different levels of the stratification variable and the number of strata equals j(113).

It is noteworthy that stratification variable is not explicitly included in the variable list but that the covariates assumed to satisfy the proportional hazards assumption, are all included in the model. In addition, the baseline hazard function ($h_{0g}(t)$) is redefined for each stratum, while, the coefficients ($B_1, B_2, ..., B_k$) are constant across the strata. The stratified Cox model will yield different estimated survival curves for each stratum because the baseline hazard functions are estimated for each stratum(113).

In the HRQL study where there are 42 subjects, 7 covariates and the strata variable is age (group 1= 57- 64 years, group 2= 57- 64 years, group 3= 65+ years).

The stratified Cox model for the HRQL Study can be written as:

$$h_1(t_i) = h_{01}(t_i) \exp(B_1 baseline\ HRQL + B_1 sex + B_2 histology + B_3 stage + B_4 liver + B_5 previous\ weight\ loss + B_6 ECOG)$$

for the stratum g=1 (patients aged less than 57 years).

Given that the covariate age has three strata *(j=3),* the stratified survival model is repeated for the remaining age groups. The covariates previous weight loss, sex, presence of liver metastases, histology, *ECOG* performance status, age and stage may influence the length of time until patient death. Given this, it is necessary to account for these factors when determining the role of baseline *FACT-G* as an independent prognostic variable for survival time. Using stratified Cox, age is accounted for as the strata variable, while the six covariates are controlled by entering them into the survival model.

2. Kaplan-Meier Method

In the HRQL study the Kaplan-Meier procedure- a nonparametric estimate of the probability of patient survival for a specified length of time, was used to calculate patient survival time(112). Kaplan- Meier is an estimation of the survivorship function that computes the proportions of surviving subjects in the cohort and these proportions are used as estimates of survival probabilities that may be observed in the population.

The focus of the survival analyses is following the progress of cases from the time of initiation (t_0) to the point where an event takes place or censoring as a marked endpoint (t_x). Specifically, the outcome of interest is patient death(113).

In the equation:

$$P_k = n_t / n_{t-1}$$

n_t = the number of subjects surviving at least until (t-1), given they survived up to the t^{th} time period and n_{t-1}= the number of subjects who are alive at the end of the (t-1) time period(113).

These proportions $P_1, P_2, \ldots, P_k$, are used as estimates of the probability that a subject from the population represented by the sample will survive time periods 1,2,3…,k respectively. The probability of surviving to time t, $S(t)$, is estimated by the product:

$$S(t) = P_1 \times P_2, \ldots, P_k$$

B. First Secondary Objective (S_1)

Seven standard clinical predictors (trichotomised age, histology, stage, dichotomised previous weight loss, sex, liver metastases, and trichotomised *ECOG* score) were entered into the logistic regression model, along with baseline HRQL in order to examine whether baseline HRQL was predictive of response to therapy.

1. Logistic Regression Model

Logistic regression is a model used to describe the relationship of several independent variables (X) to a dichotomous dependent variable(112). Logistic regression is based on a logistic function, stated by the equation:

$$f(z) = 1 / (1 + exp^{(-Z)})$$

where values of z varies from $-\infty$ to $+\infty$. When z is $-\infty$ then $f(z) = 0$, when z is $+\infty$, $f(z) = 1$. This function describes a probability- the risk of developing the disease- as a number between 0 and 1(112).

In the logistic model:

$$z = \alpha + \beta_1 X_1 + \beta_2 X_2 + ,....,+\beta_k X_k$$

z is written as the product of the independent variables of interest ($X_1, X_2, ..., X_k$) and constant repeating terms ($\alpha, \beta_1, \beta_2, \ldots, \beta_k$). This equation is substituted as the linear sum expression for z in the formula for $f(z)$:

$$f(z) = 1 / (1 + exp(-(\alpha + \beta_1 X_1 + \beta_2 X_2 + ... \beta_k X_k^{))})$$

Therefore, upon determination of the unknown parameters and values of $X_1, ... , X_k$, the probability that an individual will develop the disease over some defined follow-up time interval is obtained(112, 114).

In the HRQL Study, application of the logistic model to hypothesis S_1, defined the logistic equation as follows:

$$P(X) = 1 / [1 + exp (-(\alpha + \beta_1 baseline\ HRQL + \beta_2 age + \beta_3 sex + \beta_4 histology +$$

$$\beta_5 liver + \beta_6 previous\ weight\ loss + \beta_7 stage + \beta_8 ECOG))]$$

where patients are assessed from baseline to 3-4 cycles of chemotherapy, depending on the subject's histology.

B. Second Secondary Objective(S_2)

Seven variables (trichotomised age, stage, trichotomised *ECOG* performance status, sex, dichotomised previous weight loss, liver metastases and histology) were entered into the linear regression model along with baseline HRQL in order to examine whether baseline *FACT-G* scores were predictive of change in follow-up score.

1. Multiple Linear Regression Model

A multiple linear regression model is used to predict or estimate the value of one variable corresponding to the given values of others when the mathematical relationship between them is linear. The model is given by(114):

$$Y = a + \beta_1.X_1 = \beta_2.X_2 + ... + \varepsilon.$$

Where β is the coefficient of variability and ε represents random error. A change in the *X's* results in a corresponding change in *Y*.

In the HRQL Study, hypothesis S_2 investigated whether baseline *FACT-G* scores predicted change in follow-up *FACT-G* scores, while controlling for known clinical and demographic covariates. The best fit to follow-up *FACT-G* with baseline *FACT-G* is adjusted for the influence of each of seven covariates.

VII. RESULTS

We identified 42 patients with Stage III and IV lung cancer who presented to CCI clinics, were indexed in the ACR and had evaluable baseline HRQL. Patient biodemographics at diagnosis as well as the relationship between baseline HRQL and other patient characteristics are shown in Tables 8 and 9. In addition, Table 10 reports descriptive statistics for *FACT-G* subscales and total scores over the course of chemotherapy.

Table 10: Descriptive Statistics of *FACT-General (FACT-G)* and Subscales for Baseline and Follow-Up Assessments (n=42)

SubScales	Sample Size (n)	Mean	Standard Deviation	Median	Range Observed (min- max)
Baseline					
Physical Well-Being (PWB)	42	19.3	5.70	21.0	5.80- 28.0
Social/Family Well-Being (SFWB)	42	23.4	3.33	25.7	16.0- 28.0
Relationship with Doctor (RWD)	38	7.29	0.89	8.00	5.00- 8.00
Emotional Well-Being (EWB)	42	13.9	3.74	14.0	4.00- 28.0
Functional Well Being (FWB)	42	13.7	6.12	14.2	4.00- 28.0
Total *FACT-G* Score (TOT)	42	78.8	13.6	79.0	48.0- 107.0
Follow Up1					
PWB	40	16.8	6.13	17.0	6.00- 27.0
SFWB	40	23.2	3.97	23.3	8.70- 28.0
RWD	37	6.84	2.08	8.00	2.00- 14.0
EWB	40	14.1	4.09	15.0	4.00- 20.0
FWB	40	12.6	5.91	12.5	4.00- 20.0
TOT	40	74.2	15.54	76.25	42.6- 104.0
Follow Up2					
PWB	33	17.8	6.00	17.5	8.00- 27.0
SFWB	32	23.5	3.48	23.9	17.0- 33.0
RWD	28	6.92	1.65	7.91	2.00- 10.0
EWB	31	15.0	3.98	14.2	4.00- 20.0
FWB	31	14.2	6.47	17.7	3.00- 28.0
TOT	32	79.2	16.64	89.6	48.0- 103.0

Follow Up3					
PWB	26	17.5	6.93	16.9	3.00- 27.0
SFWB	26	23.0	3.33	22.1	3.00- 27.0
RWD	26	6.84	1.49	6.98	2.00- 8.00
EWB	26	15.3	3.70	16.4	6.00- 20.0
FWB	26	15.1	5.81	17.8	4.00- 28.0
TOT	26	78.1	15.6	86.8	48.0- 102.8
Follow Up4					
PWB	22	18.8	6.01	21.3	4.0- 27.0
SFWB	22	23.4	3.82	22.1	16.0- 28.0
RWD	19	6.78	1.71	6.42	2.00- 8.00
EWB	22	14.9	3.77	15.7	6.00- 20.0
FWB	22	14.9	6.69	18.4	2.0- 28.0
TOT	22	80.41	17.59	92.9	37.0- 106.2
Follow Up5					
PWB	19	18.6	5.56	21.6	5.0- 27.0
SFWB	19	23.4	2.96	22.8	17.0- 28.0
RWD	17	6.94	1.24	7.19	4.00- 8.00
EWB	19	15.10	3.60	17.2	6.00- 20.0
FWB	19	15.7	4.86	18.1	9.00- 27.0
TOT	19	80.95	13.47	92.4	55.0- 104.8
Follow Up6	13	17.6	3.50	17.1	13.0- 26.0
PWB					
SFWB	13	22.9	4.38	24.1	14.0- 28.0
RWD	11	7.00	1.09	7.32	5.00- 8.00
EWB	13	15.1	2.13	16.3	12.0- 18.0

FWB	13	15.0	2.13	15.7	12.0- 18.0
TOT	13	78.7	11.8	83.5	64.0- 102.0
Follow Up7					
PWB	1	17.0	--	17.0	--
SFWB	1	26.0	--	26.0	--
RWD	1	8.00	--	8.00	--
EWB	1	17.1	--	17.1	--
FWB	1	15.3	--	15.3	--
TOT	1	83.5	--	83.5	--
Follow Up8					
PWB	1	18.3	--	18.3	--
SFWB	1	26.1	--	26.1	--
RWD	1	8.13	--	8.13	--
EWB	1	16.1	--	16.1	--
FWB	1	17.3	--	17.3	--
TOT	1	85.3	--	85.3	--

A. Primary Hypothesis (P_1)

To assess the role of baseline HRQL as an independent predictor of survival, baseline *FACT-G* scores along with six covariates (sex, stage, histology, dichotomised previous weight loss, presence of liver metastases, and trichotomised *ECOG* score) were entered into the multivariate Cox regression model, stratified by trichotomised age.

The results of P_1 analysis, given in Table 11, indicate baseline *FACT-G* score is significantly associated with survival (p=0.004). The negative parameter estimate (β=-0.06) indicates that an increase in baseline *FACT-G* score corresponds to a hazard ratio less than 1 (h_z=0.94 95%CI: 0.898-0.980) or an increase in the probability of survival.

The female sex (β=-1.13) is also statistically significantly associated with a higher probability of survival (h_z= 0.32 95%CI: 0.11-0.99). The covariates *ECOG*, and presence of liver metastases also had hazard ratios less than one although they did not reach statistical significance.

Positive parameter estimates indicate an increased risk of death (hazard ratio greater than 1) or a decreased probability of survival. The covariates small cell histology (p=0.006), stage IV (p=0.001), and previous weight loss over 10 lbs (p=0.033) were all statistically significantly associated with a lower probability of survival. Hazard ratios greater than one (h_z>1) were found with respect to stage IV disease (h_z=12.55, 95%CI: 2.93-53.66), for small cell histology (h_z=5.88, 95%CI: 1.64-21.01) and for weight loss over 10 lbs (h_z=3.39, 95%CI: 1.10-10.39).

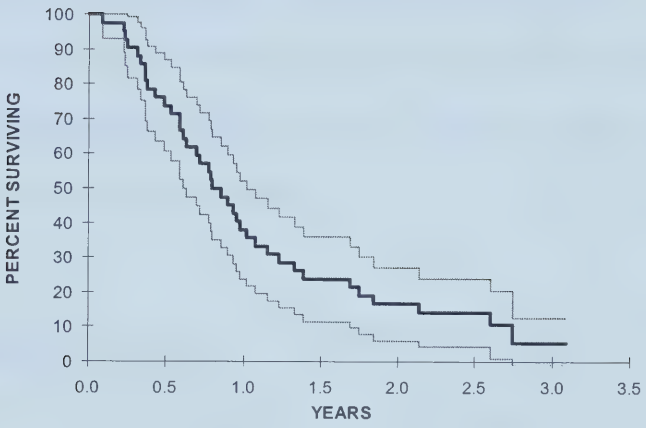
Median cohort survival was 9.87 months and 2-year survival was achieved by 7 (16.7%) patients. Four cases (9.5%) were alive at the end of study (March 31, 2001). Overall Kaplan-Meier survival with 95% confidence intervals for the HRQL cohort is shown in Figure 5.

Table 11: Cox Survival for Baseline *FACT-General (FACT-G)* Scores (n=42) stratified by Age

Variable	Coefficient (β)	Hazard Ratio (h_z)	Confidence Interval	Significance ($p < 0.05$)*
**Baseline *FACT-G*	-0.06	0.94	0.90- 0.98	0.004*
Histology				
non-small cell	1.77	1.00		
small cell		5.88	1.65- 21.01	0.006*
Stage				
III	2.53	1.00		
IV		12.55	2.93- 53.66	0.0006*
Baseline Weight Loss				
≤10	1.21	1.00		
>11		3.39	1.10- 10.39	0.03*
ECOG				
0	-0.71	1.00		
1		0.49	0.21- 1.13	
≥2		0.24	0.10- 0.56	0.09
Sex				
Male	-1.12	1.00		
Female		0.32	0.11- 0.99	0.04*
Hepatic Metastases				
None	-0.74	1.00		
Present		0.47	0.19-1.13	0.09

**Given decrease in hazard ratio is for a single unit increase in *FACT-G*

Kaplan-Meier Survival for the HRQL Cohort (n=42) with 95% C.I.



B. First Secondary Objective (S_1)

In the HRQL cohort, 35.03%(n=15) of patients recorded an increase in tumour progression and 64.97%(n=27) recorded no change or a decrease in tumour progression.

Baseline *FACT-G* scores were entered into the logistic model, along with seven covariates, stage, histology, sex, presence of liver metastases, dichotomised weight loss, trichotomised *ECOG* score and trichotomised age. However, maximum likelihood estimates could not be determined and the model results were not valid.

Consequently, univariate logistic analysis was used to describe the association between baseline *FACT-G* scores and tumour response. In the model, a positive regression coefficient (β) indicates that an increase in the level of the variable is associated with a decreased risk of tumour progression. In the HRQL study, an increase in baseline *FACT-G* scores (β= 0.72) is associated with a decrease in the patient's risk of tumour progression by 2.04 times (95%CI: 1.07-3.92).

In a supplementary analysis, chi-square analysis (Table 12) revealed a quantitatively important and statistically significant association between high and low baseline HRQL (baseline HRQL cutoffs were defined by Cella et al.(32) and tumour progression. In the HRQL cohort, almost all patients with low baseline HRQL (28/29 or 96.6%) had tumour progression and almost all patients with high HRQL (12/13 or 92.3%) had did not have progression.

Table 12: Chi-Square Analysis of Baseline *FACT-General (FACT-G)* Scores by Tumour Response ($p<0.001$)

Variables n (%)	Low Baseline *FACT-G* Score (>82)*	High Baseline *FACT-G* Score (≤82)*
no change	1 (2.4%)	12 (28.6%)
tumour progression	28 (66.6%)	1 (2.4%)

* Source: Yellen et al. J Pain Sympt Manag 13 (2) 1997: 63-97

C. Second Secondary Objective (S_2)

Baseline *FACT-G* scores were evaluated as predictors of change in follow-up score. Baseline *FACT-G* scores had a mean of 78.7 and a median of 79.0. Positive change in follow-up *FACT-G* scores (improving HRQL) were recorded in 14(34%) cases while negative change in follow-up scores (deteriorating HRQL) were recorded in 27(66%) of cases. There were no cases that recorded no change over the course of treatment. A cohort of 41 patients was analysed for S_1; patient received treatment at baseline without follow up treatment. The mean and median change in *FACT-G* follow-up score was -6.7 and -4.4, respectively recording deteriorating patient HRQL (Appendix H).

To assess the role of baseline *FACT-G* scores as a predictor of subsequent change in *FACT-G* follow up scores, baseline scores along with seven covariates (histology, stage, sex, presence of liver metastases, dichotomised weight loss, trichotomised age, and trichotomised *ECOG*) were entered into a multivariate linear regression model. The results of S_2 analysis (Table 13) indicate baseline scores were not associated with predicting change in follow up scores. The variables included in the statistical model explained only 6.1% of the variance in the dependant variable.

Table 13: Baseline *FACT-General (FACT-G)* Scores Predicting Change in Follow-up Scores using Linear Regression

Variables	Estimate (β)	Standard Error	95% Confidence Limits
Intercept (α)	5.56	30.74	-57.06- 68.19
Baseline *FACT-G*	-0.16	0.17	-0.53- 0.19
Age	-1.69	3.01	-7.83- 4.44
Sex	-0.97	5.21	-11.60- 9.65
Histology	-7.32	5.48	-18.49- 3.84
Stage	1.39	5.72	-10.26- 13.05
Hepatic Metastases	2.19	4.87	-7.74- 12.12
Previous Weight Loss	1.58	5.33	-9.26- 12.46
ECOG PSR	3.41	3.91	-4.55- 11.38

VII. Discussion

A. Review of Study Findings

The multivariate Cox analysis presented in the HRQL study reveals that there are multiple predictors of survival time for patients with advanced primary lung carcinoma. A major finding was that baseline *FACT-G* scores were statistically significantly associated with survival and, therefore, may have predictive value when used along with the current standard clinical prognostic variables.

The covariates sex, histology, stage and previous weight loss were also confirmed to be significantly associated with survival although other patient characteristics such as *ECOG* performance status and presence of liver metastases did not reach statistical significance.

Two secondary analyses were also conducted. An association was not found between baseline *FACT-G* scores and patient's response to treatment in the multivariate logistic model and was not determined in multivariate analyses. Finally, baseline *FACT-G* scores were not found to be associated with predicting change in follow up scores.

B. Primary Hypothesis (P_1)

The primary hypothesis of the HRQL study was confirmed: individuals who have lower baseline HRQL scores have shorter survival [both quantitatively important and statistically significant] than those who have higher baseline HRQL scores. While this relationship was not universally observed in the literature, this positive association has been reported in multiple studies across multiple cancer pathologies-breast(3), colon (19) malignant melanoma (22), ovarian (2), and malignant glioma (20).

This relationship has also been studied in lung cancer patients with varying stages and pathologies: in patients with inoperable lung carcinoma receiving radiotherapy (64), in patients with advanced stage NSCLC (4), in early stage carcinoma of all cell types (24) and in a cohort of heterogenous cell types and stages(115). In all of these studies, as in the HRQL study, multivariate analyses confirmed that baseline global HRQL was statistically significantly associated with the duration of survival even after adjusting for various traditional clinical covariates (age, sex, previous weight loss, performance status, presence of liver metastases, histology, stage, extent of disease). The HRQL study was undertaken in order to further investigate these relationships.

1. Clinical and Demographic Covariates as Survival Predictors (P_1)

In our study, stage and histology were two covariates strongly associated with survival. An increase in stage was associated with an increase in probability of death by 12.5 times, the highest hazard ratio of any of the binary variables entered into the model. In addition, an unfavourable histology was associated with an increase in risk of death by 5.88 times. These results, supported almost universally in the literature, serve to further confirm the value of staging and pathological information as prognostic clinical tools.

In the literature, weight loss recorded at diagnosis has been a mixed predictor of survival. The negative influence on outcome is clinically and statistically different according to the amount of weight loss reported, the statistical model used for analysis (univariate versus multivariate), and adjustment for other factors and interactions. In the HRQL study, dichotomised previous weight loss was found to be an independent predictor, statistically significantly associated with survival. Specifically, weight loss of

greater than 10 lbs was found to be associated with an increased risk of death 3.39 times that of patients who lost 10 lbs or less. Parallel results were reported by Buccheri et al.(98) where weight loss (dichotomised as present or none) in the 6 months preceding diagnosis was found to be independently influential in predicting survival, by Bernhard et al.(116) where previous weight loss $\geq$5% was independently significantly associated with survival in SCLC patients and by Skarin et al.(104) who reported weight loss of 5% or more adversely affected survival in individuals aged 40 or younger.

The published literature has also been mixed in recording the potential survival benefits for female lung cancer patients over males. In the HRQL study, female sex was associated with a decrease in risk of death by 0.32 times. Results by Bonomi et al. (101) and Albain et al.(56) confirmed our findings that the female sex is statistically significantly associated with increased survival time in lung cancer patients.

Of the covariates that were found to be statistically insignificant when entered into the Cox model (presence of liver metastases, performance status), we were most surprised to find no significant association between performance status and survival time. This is contradictory to the majority of published studies which indicate that performance status is a reliable predictor of patient outcome, both in univariate (56, 106) and multivariate models(56, 100, 106).

Our results parallel the results of Ganz et al.(4) who also found no statistical significance between performance status and survival time in lung cancer patients. It is noteworthy, however, that both the HRQL study and the Ganz study had very small patient cohorts (n=42 and n=40, respectively), while in all the aforementioned studies,

(where a statistically significant association was reported), the sample size was ≥200 patients.

2. Why is Baseline HRQL a Good Predictor of Survival? (P_1)

It is useful to speculate why baseline HRQL predicts survival. First, HRQL is a multi-dimensional construct encompassing both physical and emotional domains (11, 13, 15). Upon baseline administration, it comprehensively assesses patient well-being. However, in clinical medicine, often HRQL is assumed to be captured by measures of performance status (13) even though there is evidence that these instruments are not comprehensive enough in their scope to measure HRQL adequately. In validation studies by Cella et al.(41) strong correlations (standards for interpretation of association as defined by Cella et al.(41)) were seen between *ECOG* and *FACT-G* when evaluating physical and functional domains, but weak correlations were seen between *ECOG* and the *POMS* and *TMA* instruments evaluating emotional and social constructs. *FACT-G*, however, continued to show strong correlations with both of these tools.

These results have been mirrored in other studies. In a comparison between *EORTC QLQ-C30* and *ECOG*, moderate to strong correlations were found between physical function, role function and symptom dimensions. However, there were weak correlations between cognitive, emotional or social functioning and performance status (14). Similar findings have also been described when comparing the HRQL scales *FLIC* (15) and *Linear Analogue Self-Assessment Scale* to *KPS*.

Therefore, one might speculate that baseline HRQL is a good predictor of patient survival because it provides information about patient well-being not captured by

traditional measures. As a result, when used along with traditional clinical measures, it can be a part of more a comprehensive prediction of patient prognosis.

Second, it can be speculated that baseline HRQL is a good survival predictor because it is a patient-reported assessment of well-being. Historically, clinical observers have been reported to be poor judges of how patients feel (13, 117). Low correlations are found between patient-reported and clinician-reported overall HRQL scores, symptom subscores, physical well-being and psychologic well-being(118).

In addition, there is the perception of patients' needs going unmet as treatment decisions are made based on performance status determined by clinician judgment as opposed to patient-rated HRQL. The literature has recorded that physicians over estimated treatment toxicities of older patients even though it was younger patients who, by self-report, experienced more severe problems on the same therapy regimen (119). As a result, younger patients were consistently selected for more aggressive therapy regimens rather than older patients (17).

C. First Secondary Hypothesis (S_1)

1. Choice of Statistical Methods Used in S_1

The logistic regression model was a statistical procedure appropriate for testing hypothesis S_1 (is there a positive association between baseline HRQL and patients' response to treatment?). It was chosen because the logistic model is a powerful tool for identifying predictors of a dichotomous dependant variable in a multivariate framework. It was chosen for this study as there is a dichotomous

dependant variable (tumour progression or none), and there are numerous independent covariates that may be predictive of change in tumour progression.

When running the regression analysis, error messages resulted stating that the maximum likelihood estimates could not be determined and that the validity of model fit was questionable. These warnings were likely generated because the logistic model was over-predictive for this small cohort.

In order to comment on our hypothesis for S_1, a univariate logistic analysis was conducted. Although we could not control for standard clinical covariates, the univariate analysis confirmed associations generally found in the published literature and provided basic descriptive results that can be used to inform multivariate analysis undertaken in larger future studies.

2. Baseline HRQL Scores are Associated with Tumour Response

The first secondary hypothesis- that there is a positive association between baseline HRQL and response to treatment, when controlling for standard clinical covariates was not tested. Nonetheless, in a univariate analysis: a positive association between baseline HRQL and response to treatment was observed.

In the literature, a limited number of studies have examined this association in univariate analyses. The results of the HRQL study were supported by Ruckdeschel and Piantadosi (24) who found baseline HRQL score alone was able to predict reccurrence. These results are noteworthy as they will serve to inform hypothesis formulation and inform data analysis in future studies.

3. Supplementary Analyses

The S_1 supplementary chi-square analysis allowed us to compare the proportion of patients with high baseline *FACT-G* scores (>82) that have disease progression to those with low baseline *FACT-G* scores (≤82). Almost all patients (92.3%) who were recorded as having a response to therapy also had high baseline *FACT-G* scores. Our results support the suggestion by Cella et al. (41, 120) that a baseline score over 82 can be used as a benchmark to classify high and low HRQL scores.

D. Second Secondary Hypotheses (S_2)

The second secondary hypothesis- that there is a positive association between baseline HRQL and subsequent change in HRQL scores over the course of treatment- was not confirmed. Baseline HRQL was not found to be an important predictor of change in follow-up scores after adjustment for standard clinical covariates (*ECOG*, performance status, previous weight loss, liver metastases, age, sex, histology and stage). The results of the HRQL study do not confirm the published literature (13, 121) (122) where baseline HRQL status is prognostic of change for on-treatment HRQL. This lack of agreement in results is may be due to the small cohort used in the HRQL study.

It has been noted that this association is most evident in advanced stage cohorts. Osoba et al.(13) noted that of patients with completely resected Stage I and II malignant melanoma who were randomised to receive adjuvant therapy with either gamma interferon or levamisole, the pretreatment global HRQL scores on the *EORTC* scale were not predictive of change in on-treatment score. However, in parallel studies using

patients with advanced stage lung, breast and malignant melanoma pretreatment HRQL scores were predictive of subsequent on-treatment change in HRQL.

E. Strengths and Limitations

1. Strengths

There were several strengths of the study. First, the HRQL instrument, the *FACT-G*, was well-chosen. The *FACT-G* has, in general, performed well in distinguishing among groups and in detecting meaningful within-person change over time. This study is one of the few that have investigated the predictive validity (prognostic value) of baseline *FACT-G* scores.

Second, data collection was prospective. While the possibility cannot be excluded that baseline HRQL may be an indicator of the course of disease prior to the time of assessment, patient evaluation started before commencement of treatment thereby ensuring that measures assessed at the time were not influenced by subsequent treatment.

Third, confounders were controlled for in both the design and analysis of this study. Specifically, restriction of the study population (restricting inclusion of advanced primary carcinomas to a relatively homogeneous stage of disease) and use of multivariate analysis (controlling for potential covariates) reduced of the probability that the association we found were produced by unknown variables (109).

2. Limitations

Several limitations of our analysis are noteworthy. First, this study was limited by a small sample size. A larger sample size can reduce the probability of Type II error

(probability of failing to reject the H_0 when there is a statistically significant association between study groups)(109). While it is unlikely a larger patient cohort would change the statistical significance of the relationship between baseline HRQL and survival time, it is possible that other associations might be detected. Further investigation using a cohort of increased size appears to be warranted.

Second, the potential for inaccurate coding exists in any administrative database. Analysis and clinical information accessed from the Alberta Cancer Registry may not be as detailed as that available from chart review (123, 124). In addition, the imprecise reporting of covariates like previous weight loss may have compromised the sensitivity of our analyses.

Third, co-morbidities in the patient cohort were not recorded. This limitation is inherent in data obtained from the Alberta Cancer Registry, which does not collect such information. By not recording co-morbidities, it is possible patients whose poor baseline HRQL was due to the presence of other disease or conditions that may not have been identified. However, one could argue that co-morbidities were probably not serious in that all patients had sufficient physiological and performance status to withstand the stress of chemotherapy (125)

F. Conclusions and Recommendations

1. Conclusions

Our retrospective cohort study suggests that baseline HRQL is a statistically significant predictor of survival for patients with advanced primary lung carcinoma. When used along with traditional clinical factors, patient-reported baseline HRQL

assessment may provide additional information as to patient survival time, thereby assisting in clinical management.

Baseline HRQL score was not a predictor of tumour response. In addition, change in follow up HRQL score was not predicted by baseline HRQL.

2. Recommendations

There are several recommendations that can be made based on the results of the HRQL study. It is recommended that the secondary hypotheses warrant further study with a larger cohort. This would allow for examination of an association between baseline HRQL and tumour response and baseline HRQL and subsequent change in HRQL, while controlling for standard clinical factors.

Baseline HRQL assessment may be of benefit when used concurrently with traditional clinical assessment to assist in clinical management of lung cancer patients. The observation that the prognostic significance of baseline HRQL scores for survival remains after controlling allowance for conventional prognostic factors is a strong argument for the usefulness of HRQL instruments.

The published literature suggests several possible mechanisms that underlie the association between patient-reported baseline HRQL and survival. First, that the observed association reflects an early perception by the patient of disease progression (126), (35, 117, 121). As a result, baseline measurement may have use as a valuable additional early indicator of disease progression.

Second, it has been suggested that the physical and psychological states reflected by favourable baseline HRQL scores may influence slower tumour progression (117,

121, 126). Several preliminary studies have demonstrated an association between physical response to cancer and survival in patients with psychological support (61) (26, 127).

Cella et al.(128) recorded that patients who reported global worsening of *FACT-G* scores have considerably larger change scores than those reporting comparable global improvements. Relatively small gains in HRQL were found to have significant value and comparable declines were less meaningful. In future studies, it would be informative if baseline *FACT-G* scores can be linked with quantifiably meaningful change in follow up score. This may further support the use of baseline HRQL as an additional early predictor of disease progression and lend support to the idea of manipulating baseline HRQL as survival predictor.

Regardless of the underlying reason for the association observed between survival and baseline HRQL scores, these results suggest that HRQL measurement would be informative in routine clinical practice and future clinical trials. Further study is also warranted regarding used for baseline HRQL measurement by patients and clinicians in medical decision-making for lung cancer management.

REFERENCES

1. Coates A, Gebski V, Signorini D, Murray P, McNeil D, Byrne M, et al. Prognostic value of quality-of-life scores during chemotherapy for advanced breast cancer. Australian New Zealand Breast Cancer Trials Group. J Clin Oncol 1992;10(12):1833-8.

2. Kornblith AB, Thaler HT, Wong G, Vlamis V, Lepore JM, Loseth DB, et al. Quality of life of women with ovarian cancer. Gynecol Oncol 1995;59(2):231-42.

3. Coates A, Forbes J, Simes RJ. Prognostic value of performance status and quality-of-life scores during chemotherapy for advanced breast cancer. The Australian New Zealand Breast Cancer Trials Group. J Clin Oncol 1993;11(10):2050.

4. Ganz PA, Lee JJ, Siau J. Quality of life assessment. An independent prognostic variable for survival in lung cancer. Cancer 1991;67(12):3131-5.

5. Earlam S, Glover C, Fordy C, Burke D, Allen-Mersh TG. Relation between tumour size, quality of life, and survival in patients with colorectal liver metastases. J Clin Oncol 1996;14(1):171-5.

6. NCIC. Canadian Cancer Statistics 2001. Toronto: Canadian Cancer Society. National Cancer Institute of Canada.; 2001.

7. Cella D. Quality of Life. In: Hollan J, editor. Psycho-Oncology. New York: Oxford University Press; 1998. p. 1135-1146.

8. Au H, Palmer M. Fatigue in Patients Undergoing Chemotherapy. Edmonton: Alberta Cancer Board; 1996.

9. Blot W, McLaughlin J, Devesa S, Fraumeni J. Tumours of the Lung and Pleura. In: Schottenfeld D, Fraumeni J, editors. Cancer Epidemiology and Prevention. New York: Oxford University Press; 1996. p. 637-665.

10. Cagle P. Pathology of the Lung. In: Thurlbeck W, editor. Tumours of the Lung. New York: Thieme Medical Publishers; 1995. p. 437-551.

11. Cella DF, Cherin EA. Quality of life during and after cancer treatment. Compr Ther 1988;14(5):69-75.

12. Naughton M, Schumaker S, Anderson R, Czajkowski S. Psychological Aspects of Health -Related Quality of Life Measurement: Tests and Scales. In: Spilker B, editor. Quality of Life in Pharmacoeconomics. 2nd ed. Philidelphia, PA.: Lippincott-Raven Publishers; 1996. p. 117-131.

13. Osoba D. Lessons learned from measuring health-related quality of life in oncology. J Clin Oncol 1994;12(3):608-16.

14. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

15. Schipper H, Clinch J, McMurray A, Levitt M. Measuring the quality of life of cancer patients: the Functional Living Index-Cancer: development and validation. J Clin Oncol 1984;2(5):472-83.

16. Spilker B, Revicki D. Psychological Aspects of Health -Related Quality of Life Measurement: Tests and Scales. In: Spilker B, editor. Quality of Life in

Pharmacoeconomics. 2nd ed. Philidelphia, PA.: Lippincott-Raven Publishers; 1996. p. 25-31.

17. Schag CA, Ganz PA, Wing DS, Sim MS, Lee JJ. Quality of life in adult survivors of lung, colon and prostate cancer. Qual Life Res 1994;3(2):127-41.

18. Zaniboni A, Labianca R, Marsoni S, Torri V, Mosconi P, Grilli R, et al. GIVIO-SITAC 01: A randomised trial of adjuvant 5-fluorouracil and folinic acid administered to patients with colon carcinoma--long term results and evaluation of the indicators of health-related quality of life. Gruppo Italiano Valutazione Interventi in Oncologia. Studio Italiano Terapia Adiuvante Colon. Cancer 1998;82(11):2135-44.

19. Ramsey SD, Andersen MR, Etzioni R, Moinpour C, Peacock S, Potosky A, et al. Quality of life in survivors of colorectal carcinoma. Cancer 2000;88(6):1294-303.

20. Lovely MP, Miaskowski C, Dodd M. Relationship between fatigue and quality of life in patients with glioblastoma multiformae. Oncol Nurs Forum 1999;26(5):921-5.

21. Seidman AD, Portenoy R, Yao TJ, Lepore J, Mont EK, Kortmansky J, et al. Quality of life in phase II trials: a study of methodology and predictive value in patients with advanced breast cancer treated with paclitaxel plus granulocyte colony-stimulating factor. J Natl Cancer Inst 1995;87(17):1316-22.

22. Coates A, Thomson D, McLeod GR, Hersey P, Gill PG, Olver IN, et al. Prognostic value of quality of life scores in a trial of chemotherapy with or without interferon in patients with metastatic malignant melanoma. Eur J Cancer 1993;12(4):1731-4.

23. Portenoy RK, Kornblith AB, Wong G, Vlamis V, Lepore JM, Loseth DB, et al. Pain in ovarian cancer patients. Prevalence, characteristics, and associated symptoms. Cancer 1994;74(3):907-15.

24. Ruckdeschel JC, Piantadosi S. Quality of life in lung cancer surgical adjuvant trials. Chest 1994;106(6 Suppl):324S-328S.

25. Herndon JE, 2nd, Fleishman S, Kornblith AB, Kosty M, Green MR, Holland J. Is quality of life predictive of the survival of patients with advanced nonsmall cell lung carcinoma? Cancer 1999;85(2):333-40.

26. Kullkull W, McCorkle R, Driever M. Symptom Distress, Psychosocial Variables, and Survival from Lung Cancer. Journal of Psychosocial Oncology 1986;4(1/2)(Spring Summer):91-104.

27. Schonwetter RS, Robinson BE, Ramirez G. Prognostic factors for survival in terminal lung cancer patients. J Gen Intern Med 1994;9(7):366-71.

28. Klemm PR. Variables influencing psychosocial adjustment in lung cancer: a preliminary study. Oncol Nurs Forum 1994;21(6):1059-62.

29. Bleehen NM, Girling DJ, Machin D, Stephens RJ. A randomised trial of three or six courses of etoposide cyclophosphamide methotrexate and vincristine or six courses of etoposide and ifosfamide in small cell lung cancer (SCLC). II: Quality of life. Medical Research Council Lung Cancer Working Party. Br J Cancer 1993;68(6):1157-66.

30. Anderson H, Hopwood P, Prendiville J, Radford JA, Thatcher N, Ashcroft L. A randomised study of bolus vs continuous pump infusion of ifosfamide and doxorubicin with oral etoposide for small cell lung cancer. Br J Cancer 1993;67(6):1385-90.

31. Ginsburg ML, Quirt C, Ginsburg AD, MacKillop WJ. Psychiatric illness and psychosocial concerns of patients with newly diagnosed lung cancer. Cmaj 1995;152(5):701-8.

32. Fayers PM, Bleehen NM, Girling DJ, Stephens RJ. Assessment of quality of life in small-cell lung cancer using a Daily Diary Card developed by the Medical Research Council Lung Cancer Working Party. Br J Cancer 1991;64(2):299-306.

33. Hurny C, Bernhard J, Joss R, Schatzmann E, Cavalli F, Brunner K, et al. "Fatigue and malaise" as a quality-of-life indicator in small-cell lung cancer patients. The Swiss Group for Clinical Cancer Research (SAKK). Support Care Cancer 1993;1(6):316-20.

34. Sarna L. Women with lung cancer: impact on quality of life. Qual Life Res 1993;2(1):13-22.

35. Buccheri GF, Ferrigno D, Tamburini M, Brunelli C. The patient's perception of his own quality of life might have an adjunctive prognostic significance in lung cancer. Lung Cancer 1995;12(1-2):45-58.

36. Ringdal GI, Gotestam KG, Kaasa S, Kvinnsland S, Ringdal K. Prognostic factors and survival in a heterogeneous sample of cancer patients. Br J Cancer 1996;73(12):1594-9.

37. Cascinu S, Del Ferro E, Fedeli A, Ligi M, Alessandroni P, Catalano G. Recombinant human erythropoietin treatment in elderly cancer patients with cisplatin-associated anaemia. Oncology 1995;52(5):422-6.

38. Groopman JE, Itri LM. Chemotherapy-induced anaemia in adults: incidence and treatment. J Natl Cancer Inst 1999;91(19):1616-34.

39. Moliterno AR, Spivak JL. Anaemia of cancer. Hematol Oncol Clin North Am 1996;10(2):345-63.

40. Au H-J. Fatigue in Patients Undergoing Chemotherapy (comp 9703). In.; 1998.

41. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993;11(3):570-9.

42. Cella D. FACIT Manual: Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System (version 4): Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University; 1993 November 1997.

43. Cella DF, Jacobsen PB, Orav EJ, Holland JC, Silberfarb PM, Rafla S. A brief POMS measure of distress for cancer patients. J Chronic Dis 1987;40(10):939-42.

44. Spitzer WO, Dobson AJ, Hall J, Chesterman E, Levi J, Shepherd R, et al. Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. J Chronic Dis 1981;34(12):585-97.

45. Wright B, Linacre J. Rating Scale Analysis: Rasch Measurement. Chicago, Illinois: Mesa, Inc; 1992.

46. Cella D, Bonomi A, Lloyd S, Tulsky D, Kaplan E, Bonomi P. Reliability and Validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995;12:199-220.

47. Cella D, Hahn E, Dineen K. Meaningful Change in Cancer-specific quality of life scores: Differences between improvement and worsening. Quality of Life Research 2002;11:207-221.

48. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anaemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997;13(2):63-74.

49. Guyatt G, Townsend M, Pugsley S, Chambers L. A Measure of Quality of Life in Clinical Trials in Chronic Lung Disease. Thorax 1987;42:772-778.

50. Piper B, Lindsey A, Dodd M, Ferketich S, Paul S, Weller S. The Development of an Instrument to Measure the Subjective Dimensions of Fatigue. In: Funk S, Tornquist E, Champagne M, Archer C, Weise R, editors. Key Aspects of comfort management of pain and nausea. Philadelphia, PA: Springer; 1989.

51. Strachan R, Gebasi K. Short Homogenous versions of the Marlowe-Crowne Social Desirability Scale. Journal of Clinical Psychology 1972;28:191-193.

52. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG Performance Status Scoring in Lung Cancer: A Prospective Longitudinal Study of 536 Patients From a Single Institution. European Journal of Cancer 1996;32A(7):1135-1141.

53. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55.

54. Mulshine JL, Makuch RW, Johnston-Early A, Matthews MJ, Carney DN, Ihde DC, et al. Diagnosis and significance of liver metastases in small cell carcinoma of the lung. J Clin Oncol 1984;2(7):733-41.

55. Naughton MJ, Herndon JE, 2nd, Shumaker SA, Miller AA, Kornblith AB, Chao D, et al. The health-related quality of life and survival of small-cell lung cancer patients: results of a companion study to CALGB 9033. Qual Life Res 2002;11(3):235-48.

56. Albain KS, Crowley JJ, Livingston RB. Long-term survival and toxicity in small cell lung cancer. Expanded Southwest Oncology Group experience. Chest 1991;99(6):1425-32.

57. Buccheri G, Ferrigno D. Prognostic factors in lung cancer: tables and comments. Eur Respir J 1994;7(7):1350-64.

58. Fry WA, Menck HR, Winchester DP. The National Cancer Data Base report on lung cancer. Cancer 1996;77(9):1947-55.

59. Vigano A, Bruera E, Jhangri GS, Newman SC, Fields AL, Suarez-Almazor ME. Clinical survival predictors in patients with advanced cancer. Arch Intern Med 2000;160(6):861-8.

60. Tas F, Aydiner A, Topuz E, Camlica H, Saip P, Eralp Y. Factors influencing the distribution of metastases and survival in extensive disease small cell lung cancer. Acta Oncol 1999;38(8):1011-5.

61. Faller H, Bulzebruck H, Drings P, Lang H. Coping, distress, and survival among patients with lung cancer. Arch Gen Psychiatry 1999;56(8):756-62.

62. Kaasa S, Mastekaasa A. Psychosocial well-being of patients with inoperable non-small cell lung cancer. The importance of treatment- and disease-related factors. Acta Oncol 1988;27(6b):829-35.

63. Moinpour CM. Measuring quality of life: an emerging science. Semin Oncol 1994;21(5 Suppl 10):48-60; discussion 60-3.

64. Langendijk JA, Aaronson NK, ten Velde GP, de Jong JM, Muller MJ, Wouters EF. Pretreatment quality of life of inoperable non-small cell lung cancer patients referred for primary radiotherapy. Acta Oncol 2000;39(8):949-58.

65. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer 1994;5:635-42.

66. Kaasa S, Mastekaasa A, Lund E. Prognostic factors for patients with inoperable non-small cell lung cancer, limited disease. The importance of patients' subjective experience of disease and psychosocial well-being. Radiother Oncol 1989;15(3):235-42.

67. Sarna L. Lung Cancer. In: Hollan J, editor. Psycho-Oncology. New York: Oxford University Press; 1998. p. 340-348.

68. Kaasa S, Mastekaasa A, Naess S. Quality of life of lung cancer patients in a randomised clinical trial evaluated by a psychosocial well-being questionnaire. Acta Oncol 1988;27(4):335-42.

69. Cody M, Nichols S, Brennan C. Psychiatric Morbidity in patients with advanced lung cancer [abstract]. Quality of Life Resources 1993;2:57.

70. Thomas C, Williams T, Cobos E, Turrisi A. Lung Cancer. In: Lenhard R, Osteen R, Gansler T, editors. Clinical Oncology. Atlanta, GA: American Cancer Society; 2001. p. 269.

71. Travis W, Linder J, MacKay B. Classification, Histology, Cytology, and Electron Microscopy. In: Pass H, Mitchell J, Johnson D, Turrisi A, Minna J, editors. Lung Cancer: Principles and Practice. 2nd ed. New York; 2000.

72. Souquet PJ, Chauvin F, Boissel JP, Cellerino R, Cormier Y, Ganz PA, et al. Polychemotherapy in advanced non small cell lung cancer: a meta- analysis. Lancet 1993;342(8862):19-21.

73. Webb WR, Gatsonis C, Zerhouni EA, Heelan RT, Glazer GM, Francis IR, et al. CT and MR imaging in staging non-small cell bronchogenic carcinoma: report of the Radiologic Diagnostic Oncology Group. Radiology 1991;178(3):705-13.

74. Vansteenkiste JF, Stroobants SG, De Leyn PR, Dupont PJ, Verbeken EK. Potential use of FDG-PET scan after induction chemotherapy in surgically staged IIIa-N2 non-small-cell lung cancer: a prospective pilot study. The Leuven Lung Cancer Group. Ann Oncol 1998;9(11):1193-8.

75. Ginsberg R, Vokes E, Rosenzweig K. Non-Small Cell Lung Cancer. In: DeVita V, Hellman S, Rosenberg S, editors. Cancer: Principles and Practice. Philadelphia, PA: Lippencott Williams & Wilkins; 2001. p. 925-982.

76. Bulzebruck H, Bopp R, Drings P, Bauer E, Krysa S, Probst G, et al. New aspects in the staging of lung cancer. Prospective validation of the International Union Against Cancer TNM classification. Cancer 1992;70(5):1102-10.

77. Prasad US, Naylor AR, Walker WS, Lamb D, Cameron EW, Walbaum PR. Long term survival after pulmonary resection for small cell carcinoma of the lung. Thorax 1989;44(10):784-7.

78. Johnson BE, Grayson J, Makuch RW, Linnoila RI, Anderson MJ, Cohen MH, et al. Ten-year survival of patients with small-cell lung cancer treated with combination chemotherapy with or without irradiation. J Clin Oncol 1990;8(3):396-401.

79. Lassen U, Osterlind K, Hansen M, Dombernowsky P, Bergman B, Hansen HH. Long-term survival in small-cell lung cancer: posttreatment characteristics in patients surviving 5 to 18+ years--an analysis of 1,714 consecutive patients. J Clin Oncol 1995;13(5):1215-20.

80. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111(6):1710-7.

81. Roth J, Ruckdeschel J, Weisenburger T, editors. Thoracic Oncology. 1st ed. Toronto: Harcourt Brace Jovanovich, Inc; 1989.

82. Zelen M. Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 3 1973;4(2):31-42.

83. AJCC. Lung. Philidelphia: Lippencott-Raven Publishers; 1997.

84. Thomas P, Rubinstein L. Cancer recurrence after resection: T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1990;49(2):242-6; discussion 246-7.

85. Daly RC, Trastek VF, Pairolero PC, Murtaugh PA, Huang MS, Allen MS, et al. Bronchoalveolar carcinoma: factors affecting survival. Ann Thorac Surg 1991;51(3):368-76; discussion 376-7.

86. Harpole DH, Bigelow C, Young WG, Jr., Wolfe WG, Sabiston DC, Jr. Alveolar cell carcinoma of the lung: a retrospective analysis of 205 patients. Ann Thorac Surg 1988;46(5):502-7.

87. Grover FL, Piantadosi S. Recurrence and survival following resection of bronchioloalveolar carcinoma of the lung--The Lung Cancer Study Group experience. Ann Surg 1989;209(6):779-90.

88. Chute JP, Venzon DJ, Hankins L, Okunieff P, Frame JN, Ihde DC, et al. Outcome of patients with small-cell lung cancer during 20 years of clinical research at the US National Cancer Institute. Mayo Clin Proc 1997;72(10):901-12.

89. Ihde DC, Mulshine JL, Kramer BS, Steinberg SM, Linnoila RI, Gazdar AF, et al. Prospective randomised comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. J Clin Oncol 1994;12(10):2022-34.

90. Klasa RJ, Murray N, Coldman AJ. Dose-intensity meta-analysis of chemotherapy regimens in small-cell carcinoma of the lung. J Clin Oncol 1991;9(3):499-508.

91. Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992;327(23):1618-24.

92. Warde P, Payne D. Does Thoracic Surgery improve Survival and Local Control in limited-stage Small Cell Carcinoma of the Lung? A meta-analysis. Journal of Clinical Oncology 1993;11(2):336-344.

93. Murray N, Coy P, Pater JL, Hodson I, Arnold A, Zee BC, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1993;11(2):336-44.

94. Samet J. Lung Cancer. In: Greenwald P, Kramer B, Weed D, editors. Cancer Prevention and Control. New York: Marcel Dekker; 1995. p. 561-584.

95. Wolf M, Holle R, Hans K, Drings P, Havemann K. Analysis of prognostic factors in 766 patients with small cell lung cancer (SCLC): the role of sex as a predictor for survival. Br J Cancer 1991;63(6):986-92.

96. Evans WK, Feld R, Murray N, Willan A, Coy P, Osoba D, et al. Superiority of alternating non-cross-resistant chemotherapy in extensive small cell lung cancer. A

multicenter, randomised clinical trial by the National Cancer Institute of Canada. Ann Intern Med 1987;107(4):451-8.

97. Buccheri G, Ferrigno F. Prognostic Value of the Tissue Polypeptide Antigen in Lung Cancer. Chest 1992;101:1287-1292.

98. Buccheri G, Ferrigno D, Vola F. Carcinoembryonic antigen (CEA), tissue polypeptide antigen (TPA) and other prognostic indicators in squamous cell lung cancer. Lung Cancer 1993;10:21-33.

99. Sorensen JB, Badsberg JH, Olsen J. Prognostic factors in inoperable adenocarcinoma of the lung: a multivariate regression analysis of 259 patients. Cancer Res 1989;49(20):5748-54.

100. Rawson NS, Peto J. An overview of prognostic factors in small cell lung cancer. A report from the Subcommittee for the Management of Lung Cancer of the United Kingdom Coordinating Committee on Cancer Research. Br J Cancer 1990;61(4):597-604.

101. Bonomi P, Gale M, Rowland K, Taylor SGt, Purl S, Reddy S, et al. Pre-treatment prognostic factors in stage III non-small cell lung cancer patients receiving combined modality treatment. Int J Radiat Oncol Biol Phys 1991;20(2):247-52.

102. O'Connell JP, Kris MG, Gralla RJ, Groshen S, Trust A, Fiore JJ, et al. Frequency and prognostic importance of pretreatment clinical characteristics in patients with advanced non-small-cell lung cancer treated with combination chemotherapy. J Clin Oncol 1986;4(11):1604-14.

103. Spiegelman D, Maurer LH, Ware JH, Perry MC, Chahinian AP, Comis R, et al. Prognostic factors in small-cell carcinoma of the lung: an analysis of 1,521 patients. J Clin Oncol 1989;7(3):344-54.

104. Skarin AT, Herbst RS, Leong TL, Bailey A, Sugarbaker D. Lung cancer in patients under age 40. Lung Cancer 2001;32(3):255-64.

105. Nugent WC, Edney MT, Hammerness PG, Dain BJ, Maurer LH, Rigas JR. Non-small cell lung cancer at the extremes of age: impact on diagnosis and treatment. Ann Thorac Surg 1997;63(1):193-7.

106. Cerny T, Blair V, Anderson H, Bramwell V, Thatcher N. Pretreatment prognostic factors and scoring system in 407 small-cell lung cancer patients. Int J Cancer 1987;39(2):146-9.

107. Pujol JL, Monnier A, Berille J, Cerrina ML, Douillard JY, Riviere A, et al. Phase II study of nitrosourea fotemustine as single-drug chemotherapy in poor-prognosis non-small-cell lung cancer. Br J Cancer 1994;69(6):1136-40.

108. Verger E, Salamero M, Conill C. Can Karnofsky performance status be transformed to the Eastern Cooperative Oncology Group scoring scale and vice versa? Eur J Cancer 1992:1328-30.

109. Hennekens C, Burning J. Epidemiology in Medicine. Boston, MA: Little, Brown and Company; 1987.

110. Curran D, Fayers P, Molenberghs G, Machin D. Analysis of incomplete Quality of Life Data in Clinical Trials. In: Saquet M, Hayes R, Fayers P, editors. Quality of Life Assessment in Clinical Trials: Methods and Practice. Oxford: Oxford University Press; 1998. p. 250-280.

111. Webster K. Scoring Guidelines for FACT-An. In.; 2000.

112. Daniel W. Biostatistics: A Foundation for Analysis in the Health Sciences. 7th ed. Danvers, MA: John Wiley & Sons, Inc.; 1999.

113. Norman G, Streiner D. Biostatistics: The Bare Essentials. 1st ed. Salem, MA: Mosby-Year Book, Inc; 1994.

114. Khazanie R. Statistics: In a World of Applications. 4th ed. New York: Harper Collins; 1996.

115. Montazeri A, Milroy R, Hole D, McEwen J, Gillis CR. Quality of life in lung cancer patients: as an important prognostic factor. Lung Cancer 2001;31(2-3):233-40.

116. Bernhard J, Hurny C, Bacchi M, Joss RA, Cavalli F, Senn HJ, et al. Initial prognostic factors in small-cell lung cancer patients predicting quality of life during chemotherapy. Swiss Group for Clinical Cancer Research (SAKK). Br J Cancer 1996;74(10):1660-7.

117. Moinpour CM, Feigl P, Metch B, Hayden KA, Meyskens FL, Jr., Crowley J. Quality of life end points in cancer clinical trials: review and recommendations. J Natl Cancer Inst 1989;81(7):485-95.

118. Presant CA. Quality of life in cancer patients. Who measures what? Am J Clin Oncol 1984;7(5):571-3.

119. Kahn SB, Houts PS, Harding SP. Quality of life and patients with cancer: a comparative study of patient versus physician perceptions and its implications for cancer education. J Cancer Educ 1992;7(3):241-9.

120. Cella D. FACT-G cutoffs. In.; 2002.

121. Osoba D. What has been learned from measuring health-related quality of life in clinical oncology. Eur J Cancer 1999;35(11):1565-70.

122. Tamburini M, Brunelli C, Rosso S, Ventafridda V. Prognostic value of quality of life scores in terminal cancer patients. J Pain Symptom Manage 1996;11(1):32-41.

123. Lloyd SS, Rissing JP. Physician and coding errors in patient records. Jama 1985;254(10):1330-6.

124. Iezzoni LI. Assessing quality using administrative data. Ann Intern Med 1997;127(8 Pt 2):666-74.

125. Del Guerico L, Crohn J. Monitoring Operative Risk in the Elderly. Journal of the American Medical Association 1983;240:1350-1350.

126. Coates A. Prognostic implications of quality of life. Cancer Treat Rev 1993;19(Suppl A):53-7.

127. McCorkle R. The measurement of symptom distress. Semin Oncol Nurs 1987;3(4):248-56.

128. Cella D, Hahn EA, Dineen K. Meaningful change in cancer-specific quality of life scores: differences between improvement and worsening. Qual Life Res 2002;11(3):207-21.

APPENDIX A

THE GENERAL HEALTH QUESTIONNAIRE

(30-ITEM VERSION)

Please read this carefully:

We should like to know if you have had any medical complaints, and how your health has been in general, over the past few weeks. Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL the questions.

Thank you very much for your co-operation.

Have you recently:

olumn					
1	7. - been able to concentrate on whatever you're doing?	Better than usual	Same as usual	Less than usual	Much les than usu
2	14. - lost much sleep over worry?	Not at all	No more than usual	Rather more than usual	Much mo than us
3	20. - been having restless, disturbed nights?	Not at all	No more than usual	Rather more than usual	Much mo than us
4	21. - been managing to keep yourself busy and occupied?	More so than usual	Same as usual	Rather less than usual	Much le than us
5	26. - been getting out of the house as much as usual?	More than usual	Same as usual	Less than usual	Much le than us
6	27. - been managing as well as most people would in your shoes?	Better than most	About the same	Rather less well	Much le well
7	28. - felt on the whole you were doing things well?	Better than usual	About the same	Less well than usual	Much le well
8	30. - been satisfied with the way you've carried out your task?	More satisfied	About same as usual	Less satisfied than usual	Much le satisfi

Column						
9	31. -	been able to feel warmth and affection for those near to you?	Better than usual	About same as usual	Less well than usual	Much le well
10	32. -	been finding it easy to get on with other people?	Better than usual	About same as usual	Less well than usual	Much l well
11	33. -	spent much time chatting with people?	More time than usual	About same as usual	Less than usual	Much l than u
12	35. -	felt that you are playing a useful part in things?	More so than usual	Same as usual	Less useful than usual	Much l useful
13	36. -	felt capable of making decisions about things?	More so than usual	Same as usual	Less so than usual	Much l capabl
14	39. -	felt constantly under strain?	Not at all	No more than usual	Rather more than usual	Much m than u
15	40. -	felt you couldn't overcome your difficulties?	Not at all	No more than usual	Rather more than usual	Much m than u
16	41. -	been finding life a struggle all the time?	Not at all	No more than usual	Rather more than usual	Much m than u
17	42. -	been able to enjoy your normal day-to-day activities?	More so than usual	Same as usual	Less so than usual	Much l than u
18	43. -	been taking things hard?	Not at all	No more than usual	Rather more than usual	Much m than u
19	45. -	been scared or panicky for no good reason?	Not at all	No more than usual	Rather more than usual	Much m than u
20	46. -	been able to face up to your problems?	More so than usual	Same as usual	Less able than usual	Much l able
21	47. -	found everything getting on top of you?	Not at all	No more than usual	Rather more than usual	Much m than u
22	49. -	been feeling unhappy and depressed?	Not at all	No more than usual	Rather more than usual	Much m than u

Column						
23	50. -	been losing confidence in yourself?	Not at all	No more than usual	Rather more than usual	Much mor than usu
24	51. -	been thinking of yourself as a useless person?	Not at all	No more than usual	Rather more than usual	Much mor than usu
25	52. -	felt that life is entirely hopeless?	Not at all	No more than usual	Rather more than usual	Much mor than usu
26	53. -	been feeling hopeful about your own future?	More so than usual	About same as usual	Less so than usual	Much les hopeful
27	54. -	been feeling reasonably happy, all things considered?	More so than usual	About same as usual	Less so than usual	Much les than usu
28	55. -	been feeling nervous and strung-up all the time?	Not at all	No more than usual	Rather more than usual	Much mor than usu
29	56. -	felt that life isn't worth living?	Not at all	No more than usual	Rather more than usual	Much mor than usu
30	58. -	found at times you couldn't do anything because your nerves were too bad?	Not at all	No more than usual	Rather more than usual	Much mor than usu

FACT-An (Version 3)

Below is a list of statements that other people with your illness have said are important. By circling one number per line, please indicate how true each statement has been for you during the past 7 days.

PHYSICAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
1.	I have a lack of energy	0	1	2	3	4
2.	I have nausea	0	1	2	3	4
3.	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
4.	I have pain	0	1	2	3	4
5.	I am bothered by side effects of treatment	0	1	2	3	4
6.	I feel sick	0	1	2	3	4
7.	I am forced to spend time in bed	0	1	2	3	4

8. Looking at the above 7 questions, how much would you say your PHYSICAL WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much so

SOCIAL/FAMILY WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
9.	I feel distant from my friends	0	1	2	3	4
10.	I get emotional support from my family	0	1	2	3	4
11.	I get support from my friends and neighbors	0	1	2	3	4
12.	My family has accepted my illness	0	1	2	3	4
13.	Family communication about my illness is poor	0	1	2	3	4
14.	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
15.	Have you been sexually active during the past year? No ___ Yes ___ If yes: I am satisfied with my sex life	0	1	2	3	4

16. Looking at the above 7 questions, how much would you say your SOCIAL/FAMILY WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much so

Please indicate how true each statement has been for you during the past 7 days.

RELATIONSHIP WITH DOCTOR		Not at all	A little bit	Some-what	Quite a bit	Very much
17.	I have confidence in my doctor(s).....	0	1	2	3	4
18.	My doctor is available to answer my questions....	0	1	2	3	4

19. Looking at the above 2 questions, how much would you say your RELATIONSHIP WITH THE DOCTOR affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much so

EMOTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
20.	I feel sad.....	0	1	2	3	4
21.	I am proud of how I'm coping with my illness.....	0	1	2	3	4
22.	I am losing hope in the fight against my illness...	0	1	2	3	4
23.	I feel nervous.....	0	1	2	3	4
24.	I worry about dying.....	0	1	2	3	4
25.	I worry that my condition will get worse.....	0	1	2	3	4

26. Looking at the above 6 questions, how much would you say your EMOTIONAL WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much so

FUNCTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
27.	I am able to work (include work in home).....	0	1	2	3	4
28.	My work (include work in home) is fulfilling.....	0	1	2	3	4
29.	I am able to enjoy life.....	0	1	2	3	4
30.	I have accepted my illness.....	0	1	2	3	4
31.	I am sleeping well.....	0	1	2	3	4
32.	I am enjoying the things I usually do for fun.....	0	1	2	3	4
33.	I am content with the quality of my life right now	0	1	2	3	4

34. Looking at the above 7 questions, how much would you say your FUNCTIONAL WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much so

FACT-An (Version 3)

Please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS		Not at all	A little bit	Some-what	Quite a bit	Very much
*35.	I feel fatigued	0	1	2	3	4
*36.	I feel weak all over	0	1	2	3	4
*37.	I feel listless ("washed out")	0	1	2	3	4
*38.	I feel tired	0	1	2	3	4
*39.	I have trouble starting things because I am tired	0	1	2	3	4
*40.	I have trouble finishing things because I am tired	0	1	2	3	4
*41.	I have energy	0	1	2	3	4
42.	I have trouble walking	0	1	2	3	4
*43.	I am able to do my usual activities	0	1	2	3	4
*44.	I need to sleep during the day	0	1	2	3	4
45.	I feel lightheaded (dizzy)	0	1	2	3	4
46.	I get headaches	0	1	2	3	4
47.	I have been short of breath	0	1	2	3	4
48.	I have pain in my chest	0	1	2	3	4
*49.	I am too tired to eat	0	1	2	3	4
50.	I am interested in sex	0	1	2	3	4
51.	I am motivated to do my usual activities	0	1	2	3	4
*52.	I need help doing my usual activities	0	1	2	3	4
*53.	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
*54.	I have to limit my social activity because I am tired	0	1	2	3	4

55. Looking at the above 20 questions, how much would you say these ADDITIONAL CONCERNS affect your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much so

* These items comprise the 13-item fatigue subscale

Patient Name:_____

Patient ID Number:_____

Date (d/mo/yr):_____

Chemotherapy Cycle Number:_____

Qualitative Patient Self-Report of Fatigue Level

Instructions: Please circle the one *statement* most appropriate to you, over the past 7 days.

Compared to my last cycle of chemotherapy, I am:

more tired *as tired* *less tired*

Patient Name:_____

Patient ID Number:_____

Date (d/mo/yr):_____

Chemotherapy Cycle Number:_____

Completed by:_____

Qualitative Physician Assessment of Patient Fatigue Level

Instructions: Please circle the one *statement* you think is most appropriate for this patient over the past 7 days.

Compared to this patient's last cycle of chemotherapy, this patient is:

more tired *as tired* *less tired*

ECOG Performance Status

(Please circle one)

0: Able to carry on normal activity

1: Symptoms of disease, but ambulatory and able to carry out activities of daily living.

2: Out of bed more than 50% of time; occasionally needs assistance.

3: In bed more than 50% of time; needs nursing care.

4: Bedridden; may need hospitalization.

Heather-Jane Au

APPENDIX B

FACT-An (Version 3)

Below is a list of statements that other people with your illness have said are important. By circling one number per line, please indicate how true each statement has been for you during the past 7 days.

PHYSICAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
1.	I have a lack of energy	0	1	2	3	4
2.	I have nausea	0	1	2	3	4
3.	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
4.	I have pain	0	1	2	3	4
5.	I am bothered by side effects of treatment	0	1	2	3	4
6.	I feel sick	0	1	2	3	4
7.	I am forced to spend time in bed	0	1	2	3	4

8. Looking at the above 7 questions, how much would you say your PHYSICAL WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much so

SOCIAL/FAMILY WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
9.	I feel distant from my friends	0	1	2	3	4
10.	I get emotional support from my family	0	1	2	3	4
11.	I get support from my friends and neighbors	0	1	2	3	4
12.	My family has accepted my illness	0	1	2	3	4
13.	Family communication about my illness is poor	0	1	2	3	4
14.	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
15.	Have you been sexually active during the past year? No ___ Yes ___ If yes: I am satisfied with my sex life	0	1	2	3	4

16. Looking at the above 7 questions, how much would you say your SOCIAL/FAMILY WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much so

FACT-An (Version 3)

Please indicate how true each statement has been for you during the past 7 days.

RELATIONSHIP WITH DOCTOR		Not at all	A little bit	Some-what	Quite a bit	Very much
17.	I have confidence in my doctor(s).....	0	1	2	3	4
18.	My doctor is available to answer my questions....	0	1	2	3	4

19. Looking at the above 2 questions, how much would you say your RELATIONSHIP WITH THE DOCTOR affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much so

EMOTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
20.	I feel sad.....	0	1	2	3	4
21.	I am proud of how I'm coping with my illness.....	0	1	2	3	4
22.	I am losing hope in the fight against my illness...	0	1	2	3	4
23.	I feel nervous.....	0	1	2	3	4
24.	I worry about dying.....	0	1	2	3	4
25.	I worry that my condition will get worse.....	0	1	2	3	4

26. Looking at the above 6 questions, how much would you say your EMOTIONAL WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much so

FUNCTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
27.	I am able to work (include work in home).....	0	1	2	3	4
28.	My work (include work in home) is fulfilling.....	0	1	2	3	4
29.	I am able to enjoy life.....	0	1	2	3	4
30.	I have accepted my illness.....	0	1	2	3	4
31.	I am sleeping well.....	0	1	2	3	4
32.	I am enjoying the things I usually do for fun.....	0	1	2	3	4
33.	I am content with the quality of my life right now	0	1	2	3	4

34. Looking at the above 7 questions, how much would you say your FUNCTIONAL WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much so

***Eastern Co-operative Oncology Group (ECOG)* Toxicity Performance Status Rating**

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restriction in physically strenuous activity but ambulatory and able to carry out light or sedentary nature
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of walking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Moribund.

Source: Oken et al. Am J Clin Oncol 5 1992: 649-655

APPENDIX C

FACT-An (Version 3)

Below is a list of statements that other people with your illness have said are important. By circling one number per line, please indicate how true each statement has been for you during the past 7 days.

PHYSICAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
1.	I have a lack of energy	0	1	2	3	4
2.	I have nausea	0	1	2	3	4
3.	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
4.	I have pain	0	1	2	3	4
5.	I am bothered by side effects of treatment	0	1	2	3	4
6.	I feel sick	0	1	2	3	4
7.	I am forced to spend time in bed	0	1	2	3	4

8. Looking at the above 7 questions, how much would you say your PHYSICAL WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much so

SOCIAL/FAMILY WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
9.	I feel distant from my friends	0	1	2	3	4
10.	I get emotional support from my family	0	1	2	3	4
11.	I get support from my friends and neighbors	0	1	2	3	4
12.	My family has accepted my illness	0	1	2	3	4
13.	Family communication about my illness is poor	0	1	2	3	4
14.	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
15.	Have you been sexually active during the past year? No ___ Yes ___ If yes: I am satisfied with my sex life	0	1	2	3	4

16. Looking at the above 7 questions, how much would you say your SOCIAL/FAMILY WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10

Not at all Very much so

FACT-An (Version 3)

Please indicate how true each statement has been for you during the past 7 days.

RELATIONSHIP WITH DOCTOR		Not at all	A little bit	Some-what	Quite a bit	Very much
17.	I have confidence in my doctor(s).....	0	1	2	3	4
18.	My doctor is available to answer my questions....	0	1	2	3	4

19. Looking at the above 2 questions, how much would you say your RELATIONSHIP WITH THE DOCTOR affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much so

EMOTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
20.	I feel sad.....	0	1	2	3	4
21.	I am proud of how I'm coping with my illness.....	0	1	2	3	4
22.	I am losing hope in the fight against my illness...	0	1	2	3	4
23.	I feel nervous.....	0	1	2	3	4
24.	I worry about dying.....	0	1	2	3	4
25.	I worry that my condition will get worse.....	0	1	2	3	4

26. Looking at the above 6 questions, how much would you say your EMOTIONAL WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much so

FUNCTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
27.	I am able to work (include work in home).....	0	1	2	3	4
28.	My work (include work in home) is fulfilling.....	0	1	2	3	4
29.	I am able to enjoy life.....	0	1	2	3	4
30.	I have accepted my illness.....	0	1	2	3	4
31.	I am sleeping well.....	0	1	2	3	4
32.	I am enjoying the things I usually do for fun.....	0	1	2	3	4
33.	I am content with the quality of my life right now	0	1	2	3	4

34. Looking at the above 7 questions, how much would you say your FUNCTIONAL WELL-BEING affects your quality of life? Circle one number

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much so

APPENDIX D

Appendix D: ***Eastern Co-operative Oncology Group (ECOG)*** **Toxicity Performance Status Rating**

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restriction in physically strenuous activity but ambulatory and able to carry out light or sedentary nature
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of walking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Moribund.

Source: Oken et al. Am J Clin Oncol 5 1992: 649-655

APPENDIX E

Appendix E: TNM Definitions for Staging of Lung Cancer Tumors
Table 1: Tumor Classifications

Primary Tumor (T)	Site
T1	Tumor >3 cm or less in greatest dimension, surrounded by lung or visceral pleura, and without bronchioscopic evidence of invasion more proximal than the lobular bronchus (ie. not in the main bronchus)*
T2	Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension, Involves the main bronchus, 2 cm or more distal to the carina, Invades the visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina or associated atelectasis or obstructive pneumonitis of the entire lung
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, treachea, esophagus, vetebral, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion

Source: Oken et al. Am J Clin Oncol 5 1992: 649-655

* Note: the uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, also classified as T1.

Appendix E: TNM Definitions for Staging of Lung Cancer Tumors contd...
Table 2: TNM Classification of Regional Lymph Nodes

Regional Lymph Nodes (N)	Site
N0	No regional lymph node metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes(s)
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Source: Oken et al. Am J Clin Oncol 5 1992: 649-655

Appendix E: TNM Definitions for Staging of Lung Cancer Tumors contd...
Table 3: TNM Classifications of Distant metastasis (M)

Distant Metastases (M)	Site
MX:	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Source: Oken et al. Am J Clin Oncol 5 1992: 649-655

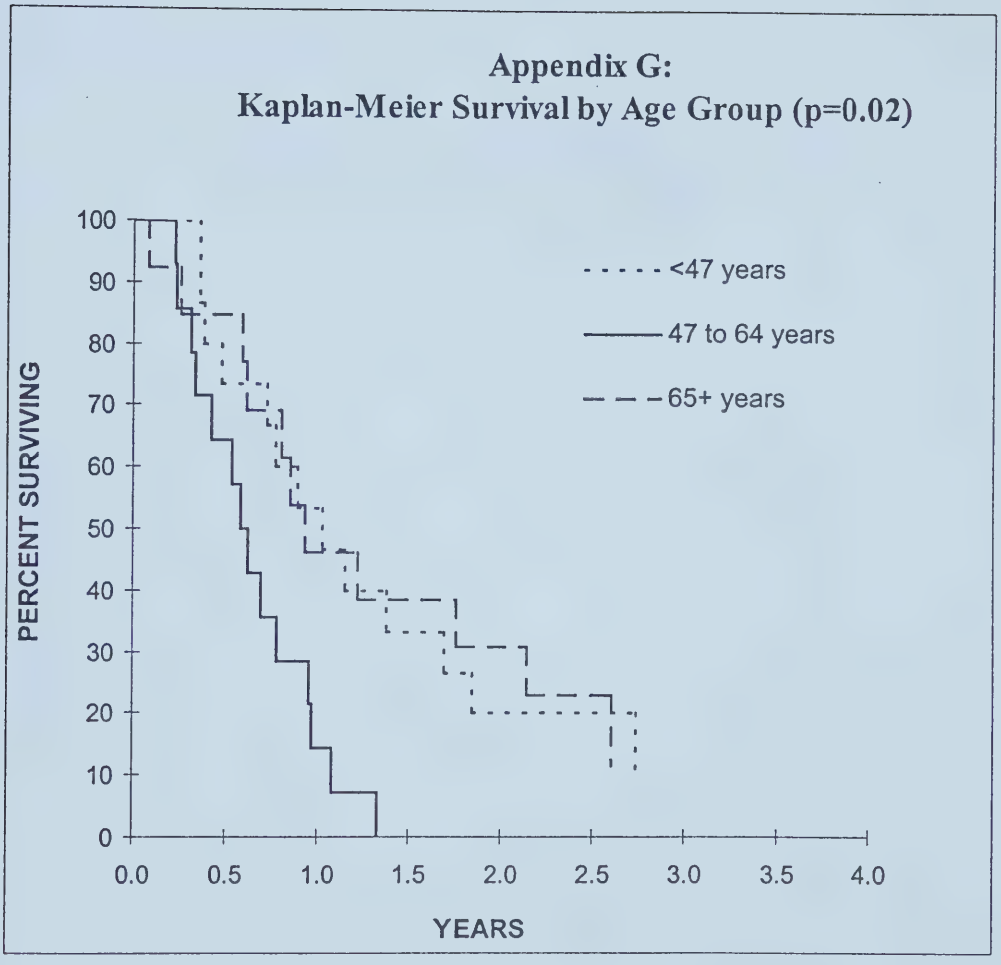
Note: M1 includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral)

APPENDIX F

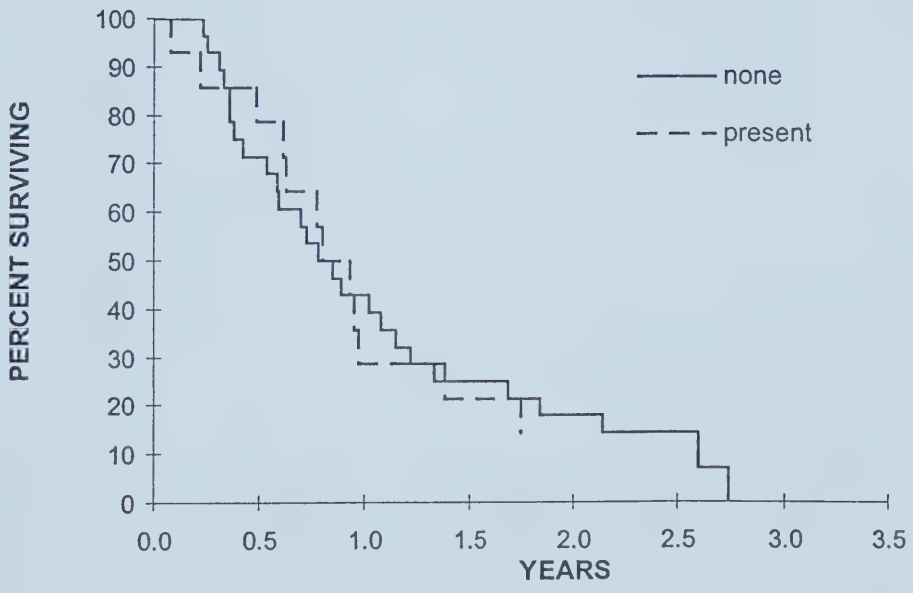
```
/   title1 'MELINA DHARMA-WARDENS: LUNG CX STUDY';

pwb_n = n(of sp1-sp7);
if (pwb_n/7 > 0.5) then pwb = sum(of sp1-sp7)*7/pwb_n;

sfwb_n = n(of ss9-ss14 ss15b);
if (sfwb_n/7 > 0.5) then sfwb = sum(of ss9-ss14 ss15b)*7/sfwb_n;

rwd_n = n(of sd17 sd18);
if (rwd_n/2 > 0.5) then rwd = sum(of sd17 sd18)*2/rwd_n;

ewb_n = n(of se20-se24);
if (ewb_n/5 > 0.5) then ewb = sum(of se20-se24)*5/ewb_n;

fwb_n = n(of sf27-sf33);
if (fwb_n/7 > 0.5) then fwb = sum(of sf27-sf33)*7/fwb_n;

tot_n = n(of pwb sfwb rwd ewb fwb);
if(tot_n/5 > 0.5) then tot = sum(of pwb sfwb rwd ewb fwb)*5/tot_n;
tot=(floor(tot*10))/10;
```

APPENDIX G

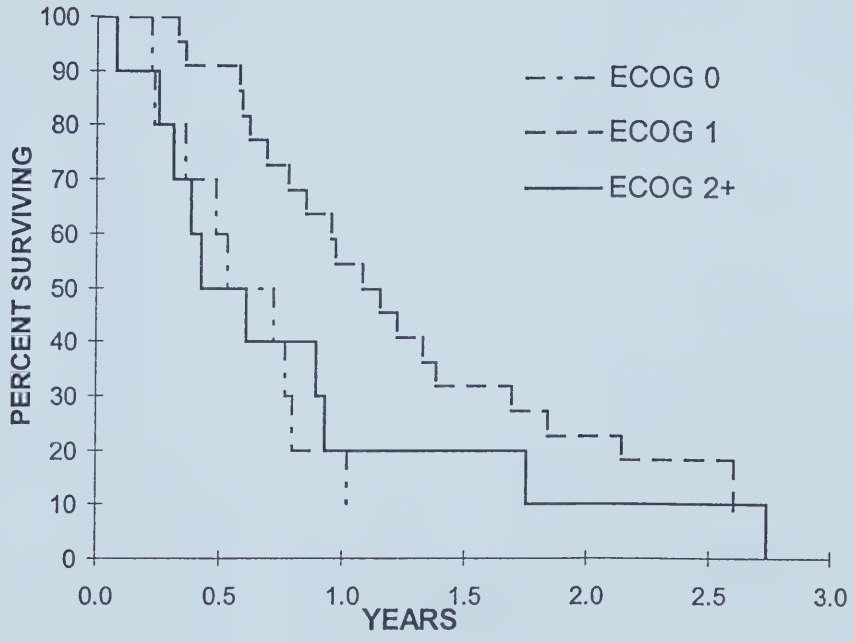
Appendix G:
Kaplan-Meier Survival by Age Group (p=0.02)



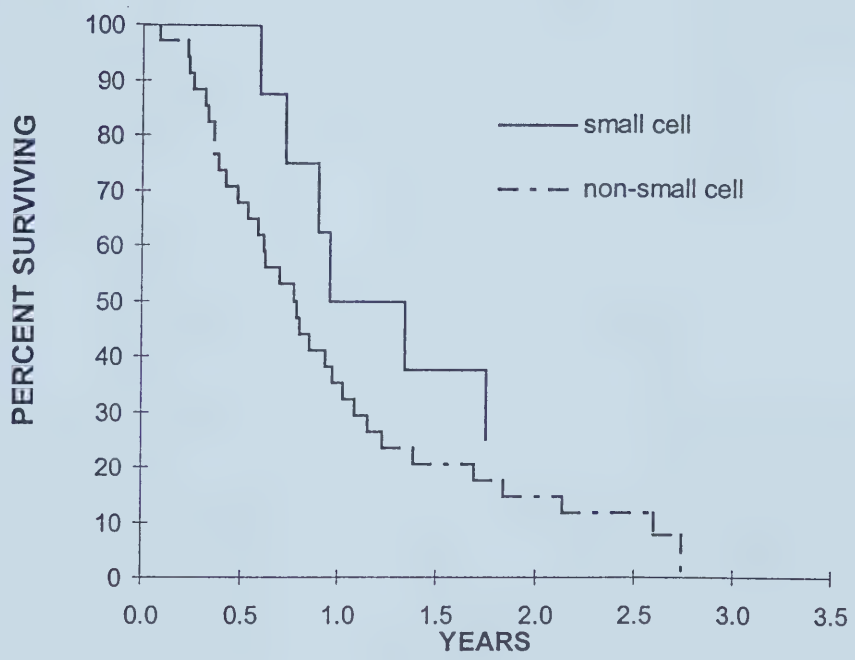
Appendix G:
Kaplan-Meier Survival by Presence of Liver Metastases (p= 0.94)



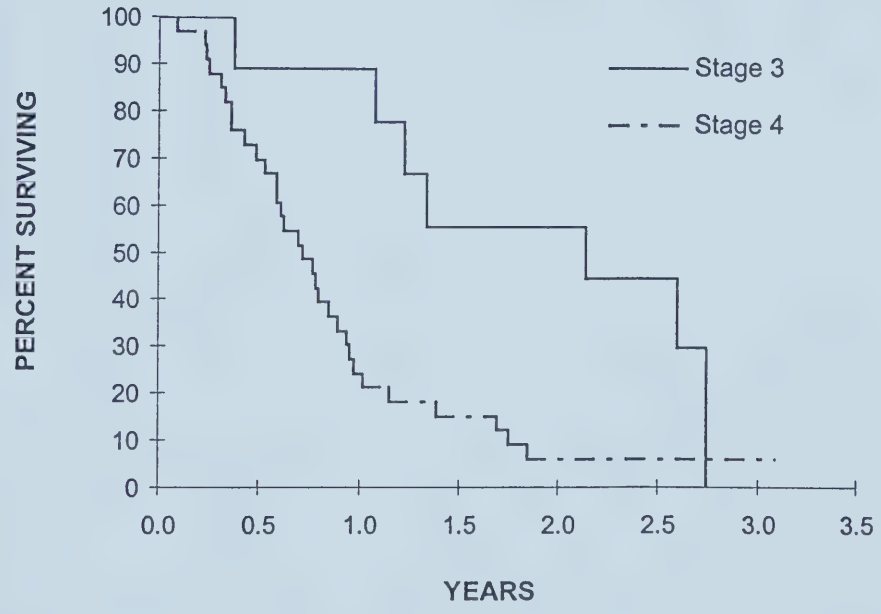
Appendix G:
Kaplan-Meier Survival for *ECOG* Performance Status Rating (p=0.16)



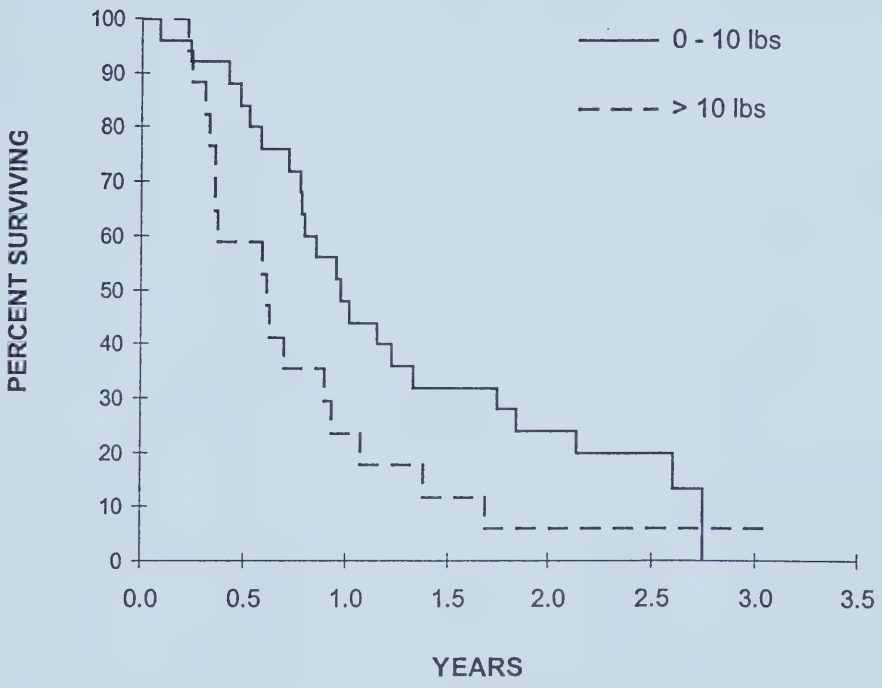
Appendix G:
Kaplan-Meier Survival by Histology (p= 0.33)



Appendix G:
Kaplan Meier Survival by Stage (p= 0.01)



Appendix G:
Kaplan-Meier Survival by Weight Loss (p=0.21)



APPENDIX H

Appendix H:
Change in Follow-up *FACT-G* Score for patients in the HRQL Cohort (n=41)